FOOD AND DRUG ADMINISTRATION

FOOD AND DRUG ADMINISTRATION SCIENCE BOARD ADVISORY COMMITTEE MEETING

8:30 a.m.

Tuesday, June 14, 2022

(Via Virtual Webcast)

10903 New Hampshire Avenue

Silver Spring, Maryland 20993

MEETING ROSTER

Designated Federal Officer

Rakesh Raghuwanshi, MPH

Office of the Chief Scientist, Office of the Commissioner, Food and Drug Administration

Science Board Members

Cynthia A. Afshari, Ph.D., DABT

Anthony Bahinski, Ph.D, MBA, FAHA

Kathryn Boor, Ph.D.

Barbara B. Kowalcyk, Ph.D. (Chair)

Richard Linton, Ph.D.

Lisa K. Nolan, DVM, Ph.D.

Theodore F. Reiss, M.D., MBE

Dojin Ryu, Ph.D.

Minnie Sarwal, M.D., DCH, FRCP, Ph.D.

Laura I. Tosi, M.D.

Connie Weaver, Ph.D.

A G E N D A

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P R O C E E D I N G S

Opening Introductions

DR. KOWALCYK: Okay. Good morning, everyone. I hope you can hear me.

Welcome to the Science Board meeting. As this is a virtual meeting, I would first like to remind everyone to please mute yourselves when you are not speaking. As this meeting is also being webcast and transcribed, please ensure you speak clearly, slowly, and state your name each time you speak so that the transcriber can accurately capture your thoughts.

If you are on mute while you're speaking, we will remind you to unmute and you can restate your comments.

My name is Dr. Barbara Kowalcyk, and I'm the Chairperson of the Science Board to the FDA and I will be chairing this meeting.

I will start by letting the Science Board members introduce themselves. I'll call on each one of you in alphabetical order by last name and will ask that you also mention your affiliation and your role at your institution. I'll begin with myself.

Again, my name is Dr. Barbara Kowalcyk. I am faculty at the Ohio State University in the Department of Food Science and Technology. I am also Core Faculty member in the Translational Data Analytics Institute at OSU and I direct the Center for Foodborne Illness Research and Prevention.

Next, I will call on Dr. Cynthia Afshari.

DR. AFSHARI: Hi, this is Cynthia Afshari. I work for Janssen Pharmaceuticals, and I'm the Global Head of Preclinical Sciences and Translational Safety.

DR. KOWALCYK: Thank you.

I will now call on Dr. Anthony Bahinski.

DR. BAHINSKI: Good morning. Hopefully that got rid of it. Unfortunately, I'm having trouble with my --

MR. RAGHUWANSHI: Oh, we can hear you fine, Tony.

DR. BAHINSKI: Excuse me?

MR. RAGHUWANSHI: We can hear you very well now.

DR. BAHINSKI: Okay, great. I'm Tony Bahinski. I'm the Chief Technology Officer for

Vivodyne and there I am in charge of bringing and implementing the high super-automated systems we're developing for 3-D human tissue chips.

DR. KOWALCYK: Thank you.

I'll next call on Dr. Kathryn Boor.

DR. BOOR: Good morning. I'm Kathryn Boor. I'm Professor of Food Science at Cornell University, also Dean of the Graduate School and Vice Provost for Graduate Education.

DR. KOWALCYK: Thank you.

I'll now call on Dr. Rich Linton.

DR. LINTON: Well, good morning, everybody. Rich Linton. I'm President of Kansas State University and the former Dean of the College of Agriculture and Life Sciences at North Carolina State University.

DR. KOWALCYK: Thank you.

Now I'll call on Dr. Lisa Nolan.

DR. NOLAN: Hi, I'm Lisa Nolan, Professor Infectious Disease and Dean of the College of Veterinary Medicine at the University of Georgia.

DR. KOWALCYK: Thank you.

I'll next call on Dr. Theodore Reiss.

DR. REISS: Hi, this is Ted Reiss here. I was most recently with a biotech company called Repertoire Immune Medicine where I was the Executive Vice President and Chief Medical Officer and Head of Development. I'm also, for the record, board advisor to Aerami, a small respiratory biotech company, and on the advisory board of a medical device company called Koneska.

DR. KOWALCYK: I'll next call on Dojin Ryu.

DR. RYU: Hi, my name is Dojin Ryu. I'm a Professor in the Department of Animal, Veterinary, and Food Sciences at the University of Idaho.

DR. KOWALCYK: Okay. Thank you.

I'll now call on Dr. Minnie Sarwal.

DR. SARWAL: Good morning. I'm Minnie Sarwal, and I'm Professor of Surgery in the Division of Multiorgan Transplantation at the University of California, San Francisco, with affiliated appointments in the Department of Medicine and Pediatrics. I also direct a Precision Transplant Medicine Program and I'm the Director of the Clearing Ground in Transplant Surgery as well as the Co-Director of the Pancreas

Transplant Program. I have consulting and following status on companies that respond out of both Stanford University where I was before as well as at UCSF in Diagnostics and Kidney Disease and Organ Transplantation. I'm delighted to be here today.

DR. KOWALCYK: Thank you.

I'll now call on Dr. Laura Tosi.

MR. RAGHUWANSHI: Laura said she might be a little delayed this morning. So we can come back to her when she hops on.

DR. KOWALCYK: Great, great. Thanks. Thank you.

Now I'll call on Dr. Connie Weaver.

DR. WEAVER: Good morning. I'm Distinguished Research Professor at San Diego State University in the College of Exercise and Nutrition Science.

DR. KOWALCYK: All right. Thank you.

I don't believe there are any other FDA Science Board members on the call. Did I miss anyone? Okay. Then we'll move along. Thank you, everyone.

So our goal is that today's meeting will be a fair and open forum for discussion of the agenda

topics. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair.

If you wish to speak, simply use the Raise Hand function in Zoom to get my attention. Rakesh will also assist me in recognizing speakers. If I miss you, feel free to unmute yourself and get my attention.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

Now I'll pass it to Rakesh Raghuwanshi who will provide some information about Conflicts of Interest.

Rakesh?

Conflict of Interest

MR. RAGHUWANSHI: Thank you, Barb, and good morning to all of you. It is so nice to be able to see you again, having been knee-deep in the pandemic for the last two years. We haven't had too much of a chance to interact and hopefully this fall we'll be

able to see you all in person for an in-person meeting.

I'd like to welcome the members of the Science Board, the public, and the FDA staff members to today's meeting.

Today, the Science Board will consider Challenges in Evaluating the Safety of Dietary Supplements and Food Ingredients with Predicted Pharmacological Activity Utilizing Cannabinoids as a Case Study.

The Science Board will also hear about the agency's enhanced efforts to spur the development, qualification, and adoption of new alternative methods for regulatory use that can replace, reduce, and refine animal testing and have the potential to provide both more timely and more predictive information to accelerate product development and enhance emergency preparedness.

Lastly, the Science Board will hear about the agency's efforts to ensure optimal organization, infrastructure, and expertise for data science efforts in alignment with its regulatory scope and evidence-based decision-making in support of FDA's public health

priorities.

All members of this advisory committee are special government employees and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Based on the agenda for today's meeting, no conflict of interest waivers have been issued in connection with this meeting.

We have an Open Public Comment period scheduled for 11 a.m. with seven members of the public having signed up to speak.

For our members and other panelists, please remember to unmute yourselves when you're speaking and mute yourselves when you are not speaking to help minimize any background noise so that our transcriber can pick up all that is being stated.

Thank you so much for taking the time to be here today and taking part in the Science Board meeting.

Barb, I'll turn it back over to you now.

DR. KOWALCYK: Thank you very much.

We're going to jump right into things this morning. The first topic is New Alternative Methods and we are very glad to have Drs. Janet Woodcock, David Strauss, and Jacqueline O'Shaughnessy here with us today.

Before they begin their presentation, I'd like to request that each one of you please introduce yourselves for the record and briefly describe your role at the agency, starting with Dr. Woodcock, then Dr. Strauss, and then Dr. O'Shaughnessy.

I would like to make sure to note that we do look forward to hearing more from you, Dr. O'Shaughnessy, at our next Science Board meeting this fall to learn more about your efforts within the Office of the Chief Scientist, which is an integral part of FDA, and also to get to know you better.

So I will now pass this over to Dr. Woodcock.

DR. WOODCOCK: Thank you.

I'm Janet Woodcock. I'm currently the Principal Deputy Commissioner at FDA and I am very happy to meet this distinguished panel and I think we are bringing some real tasty issues for you to wrestle with scientifically today.

Jackie?

DR. O'SHAUGHNESSY: Hi, good morning. I'm Jackie O'Shaughnessy. I'm currently serving as FDA's Acting Chief Scientist and I began serving in this role when Rear Admiral Denise Hinton began her appointment as the Deputy Surgeon General last fall.

I, of course, want to thank, as well as Dr. Woodcock had just mentioned, the efforts of the Science Board members really for your time. We're, of course, grateful for your service and, of course, the Office of the Chief Scientist has and is continuing to advance all of these efforts as related to our first topic today on the New Alternative Methods and really look forward to the opinions and discussion.

Thank you.

David?

DR. STRAUSS: Good morning. I'm David Strauss. I'm Director of the Division of Applied Regulatory Science in the Center for Drug Evaluation and Research at FDA, and I am presenting today on behalf of a group that spans all of the Product Centers at FDA and is on the New Alternative Methods Initiative and I'm looking forward to talking to you further about that in a minute.

DR. KOWALCYK: Okay. Dr. Woodcock, would you like to make your presentation?

DR. WOODCOCK: Certainly. Well, I'd just like to make an introduction to this first topic which is about the qualification of New Alternative Methods.

I noticed when people introduced themselves that many of you were involved in translational science and at least at FDA translational science involves evaluation of evolving products and technologies and we must use evaluative tools or translational tools, right, that help us determine what the performance characteristics are of the new method or whatever and, you know, how reliable it is, how predictive it is for

use in making regulatory decisions.

And so the question arises how will you get on the path from a new alternative method of some type, a new evaluative method that has been developed, whether it's a patient-reported outcome, a new biomarker, a new kind of clinical trial design, or some type of test that might replace or refine animal tests?

A tremendous amount of work has gone into the new alternative methods space internationally, in the U.S. FAAM has looked at this, the National Academies have looked at this, certainly the FDA, and there's a wide range of government efforts. There's been many technologies developed, such as NIH, for example, is very interested in organs on a chip, as everyone knows, and these have a wide variety of potential applications.

But to move any of those from point of a new technology that's been developed that perhaps is standardized somewhat to something that actually can be used in regulatory decisions that impact human lives, there's a big gap.

We have been working over the years in

certain areas, and Dr. Strauss will go into this in more detail, but, for example, in the biomarker area and tissue-reported outcomes area and so forth on what we call qualification process and that is a way to rigorously determine the performance of a new evaluative method or we call it TOOL, the new TOOL, and see what it can do and to what extent can you rely upon it for making a decision in the specific context of use.

We call that process qualification. If something becomes qualified for a specific context of use, then in fact developers or others can use this tool without having to reprove its validity or reliability in their circumstances, as long as they stick to the particular use the tool was qualified for.

Now this is something difficult to get one's head around and this is why we're giving an introduction only at this meeting and hope to have an ongoing engagement with the Science Board about this topic because reducing, refining, and replacing a current battery of toxicology tests that are used in a variety of evaluations, everything from contamination

by chemicals in the food supply to drug development to compatibility and testing for devices and so forth, we do need new tools and we're very eager to have new tools but those tools have to be fully vetted and it is a fairly rigorous process.

So what we would like to do is really initiate a process and get going on this because a tremendous amount of science has been done. There are many tools out there. They've reached some degree of standardization and reliability and so I think now is the time to start really looking at can we qualify them for various uses and those uses are everything from lot release tests all the way through to the toxicology tests that are used for, say, drug development to first-in-humans and so forth.

So with that, I'll turn it over to Jackie O'Shaughnessy. Dr. Strauss is going to go over this in much more detail, but I wanted to give a broad framework first.

Thanks.

DR. O'SHAUGHNESSY: Thank you very much, Dr. Woodcock. Greatly appreciate, of course, all of your

remarks this morning and really do at this point would like to turn it over to David to get him to start the presentation and discussion for everyone.

Thank you.

DR. STRAUSS: Okay. I'm getting my screen share going. Okay. Are you seeing slides?

DR. KOWALCYK: Yes, we are.

MR. RAGHUWANSHI: We see them, David.

DR. STRAUSS: Okay. Very good. Thank you.

All right. So I'm going to be presenting today, as just introduced, on Advancing Alternative Methods for Regulatory Use.

My name's David Strauss. I'm Director of the Division of Applied Regulatory Science in CDER, but I'm presenting today on behalf of the FDA New Alternative Methods Group that's come together around this topic, and I would like to thank all the members of this group that Dr. O'Shaughnessy and I have been co-leading. We have members from all the different Product Centers, as shown here.

Here's a key to the abbreviations. We will be using these abbreviations in the talk but not too

much. There are other members from other parts of the Office of the Commissioner that are also a part of this group.

Why are we here? Well, as Dr. Woodcock briefly introduced, we plan to seek input from the Science Board on how the agency can enhance its existing approaches to support the development, qualification, and implementation of alternative methods for regulatory use that can address the so-called three Rs of animal testing, replace, reduce, and refine, and improve predictivity of non-clinical testing.

The purpose of today's presentation is to introduce the topic. We're not seeking specific detailed feedback from the FDA Science Board today, but we would like to charge a Science Board subcommittee to work on this topic and the subcommittee's report would be presented at a future Science Board meeting.

The outline for out talk is to cover a background, introduce FDA's proposed New Alternative Methods Program, discuss FDA product areas specific consideration, foods, drugs, medical devices, tobacco,

etcetera, then discuss new alternative methods applied research and examples of alternative methods use in regulatory submissions, and, finally, summarize and discuss next steps.

We have a broad mission at FDA. It includes ensuring the safety of food supply, cosmetics, products that emit radiation, the safety advocacy and security of human and veterinary medical products, drugs, biologic products, medical devices, regulating the manufacturing, marketing, and distribution of tobacco products, not just traditional tobacco products but newer types, as well, and fostering development of medical products to respond to deliberate and naturally emerging public health threats, and FDA's mission is at the core of what we do.

Animal testing has played an important role in fulfilling FDA's mission. As an example, in the medical product development space, FDA reviews medical product developers' submitted data to establish under what conditions a new medical product can be safely administered to patients, whether some new medical products carry an increased risk for developmental and

reproductive toxicity or an increased cancer risk, and this includes endpoints that cannot ethically be obtained in humans, such as histopathological analysis of all major organs. This is many organs that are looked at and also blood chemistries of how organs talk to each other and animal studies play a critical role to meet this need and bring safe and effective therapies to patients.

At the same time, we have a longstanding commitment to replace, reduce, and refine animal testing. A little bit more detail about the three Rs, replacing, that's a test method that substitutes traditional animal models with other test systems. This can include cellular in vitro methods. It can include in silico computer methods.

Reducing, where a test method decreases the number of animals required for testing, and refining, where a test method eliminates pain or distress in animals or enhances animal well-being.

New alternative methods incorporate the three Rs. We have had successes to date with the three Rs. One example in the drug and biologic space is the

International Council for Harmonization, ICH, of the Technical Requirements for Pharmaceuticals. Prior to these guidelines, separate animal studies were often required for developing drugs and biologics in different countries and regions and so creation of ICH, which happened in the 1990s and then over the past decades implementation of many different harmonized guidelines, has reduced animal testing by decreasing repeat animal studies that may occur in different countries or regions and standardizing the timing of when studies should be conducted. So they are not done unnecessarily or earlier and you wait until you need them for critical decision-making.

There are other organizations with similar themes relevant to other product areas. There's a Veterinary Medicine ICH. There's an International Collaboration on Cosmetics Regulation, an International Organization for Standards, ISO, develops standards for applied medical devices and other product areas.

We also had successes with interagency coordination and collaboration. We play an active role in the Interagency Coordinating Committee on the

Validation of Alternative Methods or ICCVAM. There are many U.S. Federal Government agencies involved in ICCVAM and ICCVAM coordinates activities within the Federal Government relevant to new test method of evaluation, acceptance, and use, and ICCVAM-coordinated activities have led to the acceptance of alternative methods for testing some FDA-regulated products, and we will talk more about that in a minute.

One is paralytic shellfish toxin detection where in vitro assays in 2013 were listed as approved methods for the National Shellfish Sanitation Program Guide in place of an animal test.

In the drug space, Botulinum Neurotoxin Type A, which is used for both cosmetic reasons and for treating certain medical illnesses or diseases, and you need to assess the product's stability and potency, and FDA accepted an in vitro method in 2012 for testing the stability and potency of drug products in place and the median lethal dose method in rodents.

With regard to pyrogen testing, these are endotoxin substances that cause fever, FDA guidance in 2012 discussed approaches that could reduce animal use

and indicated an in vitro method may be used instead of an animal test with appropriate product-specific validation. There's more details in the guidance and there are also links here to the ICCVAM website that has a database and accepted of alternative methods. You can search for FDA and additional ICCVAM resources on some of the topics discussed here.

In Toxicology Assessment in the Drug and Biologic Development space, a guidance, ICH guidance released in 2015 introduced a step-wise approach for employing physiochemical and in vitro methods for photo-safety evaluation of pharmaceuticals that can be completed without the use of animal studies for assessing eye irritation and skin sensitization for pharmaceuticals, reconstructed human corneal-like epithelium, and 3-D reconstructed human epidermis models replaced rapid tests for eye irritation and skin sensitization, and there are multiple other ICH and FDA guidance documents with three R principles where there are topics of decreasing certain standalone animal studies, to reduce the number of animal studies, delay certain studies until later in drug development, and

guidances discuss the role of in vitro and silico methods, and there are links to a couple of FDA articles that have more resources and discuss this in more detail.

Transforming toxicology is a key goal for us at FDA. There was an Advancing Regulatory Science Plan in 2011 and the first listed priority was modernizing toxicology to enhance product safety. There was a Predictive Toxicology Roadmap in 2017, and a report released on Advancing New Alternative Methodologies at FDA in 2021.

We have multiple cross-agency working groups, including members from across the Product Centers, and the Toxicology Working Group, Alternative Methods Working Group, Modeling and Simulation Working Group. We also have Applied Regulatory Science Work throughout the agency, we'll talk a little bit more about that, and national and international collaborations, as I just discussed, examples of ICH and ICCVAM, are critical.

There's a lot of excitement about new technologies. This includes advances in systems

biology, stem cells, engineered tissues, mathematical modeling, to present new opportunities to improve our ability to predict risk and efficacy. This includes micro-physiological systems, combined in vitro and in silico models that can predict safety or efficacy in patients, genetically engineered cellular models that can predict efficacy in patients, such as for certain types of rare genetic diseases, and advances may help bring products to market faster with improved efficacy for medical products and also to prevent products with increased toxicological risk from reaching the market.

However, I want to stress, and as Dr. Woodcock mentioned, there are multiple steps required to translate these new technologies into regulatory use and maintain the same standard of safety, efficacy, and quality of FDA-regulated products, our core mission.

I'll talk more about context of use and some of these other aspects here that are critical to introducing new methods to use around the world for product development.

While we are nowhere near being able to replace all animal testing, there are opportunities for

alternative methods to make additional inroads in addressing the three Rs for specific context of use, a critical part we'll also talk about more.

I'm now going to transition to FDA's Proposed New Alternative Methods Program. In the Fiscal Year 2023 President's Budget that has been released, there's a link. It proposes new funding to implement a cross-agency New Alternative Methods Program at FDA to spur the adoption of new alternative methods for regulatory use that can replace, reduce, and refine animal testing and improve predictivity of non-clinical testing to streamline development of FDA-regulated products, bring products to the U.S. public and patients more rapidly, more efficiently, and ensure these products are safe, effective, and that patients can depend on them.

This program will be essentially coordinated through FDA's Office of the Chief Scientist with FDA centers implementing agency-wide programmatic objectives.

We cannot develop and implement alternative methods alone. So through this initiative, we will expand processes to qualify alternative methods for

regulatory use. That's the top of this triple venn diagram on the right. On the left, provide clear guidelines to external stakeholders developing alternative methods and on the right fill information gaps with applied research to advance new policy and guidance development.

As we have already stressed, collaborations with external stakeholders are vital, including our federal partners, public/private partnerships, including industry scientists, academic scientists, and international regulators.

Why the focus on qualification? I'm going to discuss examples of our medical product development tool qualification programs. Medical product developers can submit data from alternative methods in investigational drug and device applications or marketing applications.

However, if it comes from a new method, an alternative method, the suitability of the alternative method would need to be evaluated in parallel and there typically isn't time to do this and it introduces significant uncertainty for the medical product

developer.

So qualification is a process that allows for an alternative method to be endorsed by FDA in advance for a specific context of use. The qualified context of use defines the boundaries within which the available data adequately justify use of the tool and this is a similar concept to a drug or medical device's indications for use that defines which patients can receive that therapy.

In addition, medical product developers can then use the alternative method for the qualified context of use with confidence that it is an acceptable method.

We have current FDA qualification programs in drugs and biologics, the drug development tools qualification programs, including biomarker qualification where alternative methods can be qualified, and a new pilot program that I'll talk about more in a minute.

In devices in CRH, Medical Device Development Tools Qualification Program, there is a specific category of non-clinical assessment models. There's

additional information, including qualified tools, on FDA's website, and introduces the question of whether there's a role for qualification programs in other FDA product areas.

A little bit more detail on the qualification process. It differs a little bit between CDER/CFER and CRH. This is the CDER/CFER process. It starts with a letter of intent that initiates the qualification process of a biomarker if you're doing biomarker qualification for a proposed context of use in drug development. This is reviewed by FDA and if accepted, it then would go to the stage of a qualification plan that defines the intended development to generate the necessary supportive data to qualify the biomarker for the proposed context of use.

This is also reviewed by the agency and then goes on to a full qualification package that the submitter would develop that contains all the accumulated data to support the qualification of the biomarker for the proposed context of use.

This comes into the agency and there is then a recommendation that contains FDA's determination on

whether the biomarker is qualified for the proposed context of use, based on a comprehensive review of the qualification package.

In addition to the previously existing qualification programs in CDER/CFER, we in the past year or so introduced the Innovative Science and Technology Approaches for New Drugs or ISTAND Pilot Program. It's designed to expand drug development tools types to those outside of scope of the other programs, and on our website we call out that this as examples can include micro-physiological systems to assess safety or efficacy questions and development of novel non-clinical pharmacology and toxicology assays.

As I'll talk about an example, alternative methods can go through biomarker qualification, as well, if there is a biomarker output.

On the devices side with the CHR Qualification Program, the non-clinical assessment model is a non-clinical test model or method that measures or predicts device function or in vivo device performance and this can be used to reduce or replace animal testing or reduce test duration or sample size.

For more information about medical device development tools, there's a link. An example of a medical device development tool is the virtual population, a set of anatomically-correct whole body models for thermal and electromagnetic fluid dynamic simulations, important for certain clinical devices, and there's a link where you can learn more.

As a part of the plan, we talked about policy and guidance to streamline qualification and implementation, and what do we mean by this? This can be guidance on qualification processes.

We have guidances in CDER/CFER and CHR on the respective qualification processes. It can include topical guidances on specific safety or development areas and we'll talk about more examples and guidances on assessing credibility of specific types of alternative methods or what to include in regulatory submissions. This can be very important for facilitating the use of new methods.

As examples, in devices there is a guidance on assessing the credibility of computational modeling and simulation in medical device submissions, and in

the Center for Drugs we have a guidance on computational and silico physiologically-based pharmacokinetic analyses that describes the format and content of how data using these methods should be submitted to the agency so we can easily and rapidly review that data.

A question of whether there'd be a role for micro-physiological systems or other complex in vitro models-related general considerations guidances.

I'm now going to talk about two case studies highlighting components of the FDA New Alternative Methods Program Plan, highlighted against in this venn diagram on the right, one related to cardiac safety and the other developmental and reproductive toxicity.

The first example will highlight how filling information gaps with applied research can lead to policy and guidance that ultimately streamline qualification and implementation.

This relates to the poor rhythmic risk or abnormal heart rhythm risk that drugs can cause and led to many drugs being removed from the market in the 1990s and early 2000s and then regulatory guidelines

relied on a non-specific test for predicting drug-induced abnormal heart rhythms, and a consortia came together developing the so-called Comprehensive In Vitro Poor Arrhythmia Assay or SIPA that used laboratory cell-based models combining information together in systems pharmacology integrated computer models to predict a poor arrhythmic risk or heart safety in patients.

There was a systematic process over a number of years of significant FDA-applied research in collaboration with consortia and then leading to workshops, white papers, and ultimately new guidance. The type of applied research is defining assay standards, best practices, variability, how to develop, optimize, validate models, and best practices for new types of assays, such as induced pluripotent stem cell or IPSC-derived cardiomonocyte assays.

An example of a collaborative multisite study that was supported through a FDA broad agency announcement award to a consortia and it resulted in an international multisite study of human IPS-derived cardio-monocytes for drug poor arrhythmic potential.

This includes ten sites from around the world using consensus protocol, standard blinded drugs across multiple continents, and that is how we can get the data to understand these new technologies for potential regulatory use.

There were collaborative workshops. This was a summary of a workshop that occurred in 2018 and after that workshop there were white papers that developed, one on human stem cell-derived cardiomonocyte assays, had broad authorship from many different groups.

There was another white paper on cardio-arrhythmia model validation. This included silico computer models that the principals applied to in vitro models or other model types.

Over the past three and a half years, we updated the clinical and non-clinical guidelines for priori risk potential, the ICH guidelines, and these new guidelines include best practice recommendations for in vitro ion chain and human IPS stem cell assays to enable use as follow-up studies in place of potential animal studies and principals for validating priori rhythmic models and qualifying them for

regulatory use which can reduce animal use.

The second case study highlighted policy and guidance to streamline qualification and implementation and how we have now accepted an alternative method into our qualification program and this is specifically related to reproductive and developmental toxicity and that ICH guideline revised in 2020 contains a new section on novel testing paradigms and regulatory acceptance of alternative assays supporting the three Rs.

It describes circumstances under which qualified alternative assays can be used. No specific assays are recommended but basic scientific principles are included to assist in assay qualification for regulatory use and there's an extensive annex, including reference compounds, for assessing alternative assays and this can be updated as new information comes along.

As I mentioned, we have accepted into our Biomarker Qualification Program an alternative method that, put up the context of use in a minute, has been accepted at the letter of intent stage. It's pending

submission of a qualification plan, and in the Drug Development Tools Qualification Programs, as a part of the 21st Century CURES Act, there were transparency requirements and so all submitted letters of intent qualifications plans and etcetera and FDA's responses go up on FDA's website and you can read more about them.

The proposed context of use's safety biomarker for detecting human developmental toxicity potential in vitro using pluripotent stem cells at the non-clinical stage of drug development for small molecule drugs as a part of weight of evidence approach as described in that ICH guideline.

Now we're going to transition to additional FDA product areas specific considerations.

We have not talked about tobacco much yet, but this is a very interesting and complex area. FDA regulates both traditional tobacco products and newer products, such as e-cigarettes.

This image from a FDA article shows the diversity of tobacco products that the agency regulates, traditional tobacco products and newer so-

called deemed tobacco products, and this article outlines how we need alternative methods relevant to target tissues for tobacco product exposure. The obvious one is a lung and I'll talk more about lung micro=physiological systems in a little bit.

With veterinary medicines, there are some different considerations. Animals are the patients. However, there are still opportunities to address the three Rs. Developing generic animal drugs for non-systemically-absorbed drug products has required clinical endpoint bioequivalence trials for every indication.

At the Center for Veterinary Medicine FDA is developing roadmaps for alternative approaches to bio-equivalence evaluation on these various types of products. This includes understanding drug physio-chemical properties, formulation, critical quality attributes, and use of physiologically-based pharmaco-kinetic models.

I earlier put up the FDA guidance document from CDER on PV/PK models and these concepts here are similar to what has been implemented and we continue to

try and implement in the Center for Drugs for generic drugs and reducing the need for clinical outcome studies.

In the food space, for measuring botulinum neurotoxin and contaminated foods, the standard method has relied on a mouse assay that can use large number of animals and a proposed alternative is in vitro approaches to detect the presence and potency of the neurotoxin.

In the cosmetics space, here is an article that includes FDA authors. It discusses next generation risk assessment. This is exposure-led hypothesis-driven approaches, and there's a need to develop and test in vitro and silico approaches to enable confident application in a regulatory context.

With product quality, and here specifically related to biologics and vaccines, detecting viral agents and biologics, biomanufacturing is very important. Standard methods have relied on multiple animal-dependent assays and a proposed alternative is to use next generation sequencing to detect viral advantageous agents.

With potency testing of human and veterinary rabies virus vaccine, this has relied on mice and is variable and time-consuming, and there are efforts to look at highly-specific monoclonal antibodies to quantitate key parts of the vaccine that could replace animal testing.

With regard to next generation sequencing to detect viral agents, there was a workshop co-sponsored by FDA and NIST, National Institutes of Standards, on this topic, and there's a link to that article here.

With medical devices, there was a workshop on new alternative methods and new approach methodologies for medical devices and at that workshop, there's also a link here, there were FDA talks on medical device development tools and bio-compatibility considerations, in vitro thrombogenicity evaluation of medical devices, regulatory considerations, and ongoing research efforts.

And in the drug space, this article, there have been links to this earlier, describes opportunities and challenges of using NAMs in drug development for regulatory purposes, and this

additional article describes events and activities that have had the greatest impact on animal use and ongoing efforts and opportunities.

We're now going to `discuss new alternative methods applied research and examples of its use in regulatory submissions.

We have cross-cutting FDA-applied research in, as we'll highlight here, lung micro-physiological systems as an example. There's tobacco-focused research with the Center for Tobacco Products and FDA's National Center for Toxicological Research, NCTR.

There's also applied research with lung micro-physiological systems related to devices, and there are other applied research activities in this area in drugs, biologics, and related to medical countermeasures.

The liver is a very important organ system. Liver toxicity has been a major reason for discontinuation of drugs from development and chemical contaminants in food can also cause liver toxicity. The liver is critical for drug and food metabolism.

We've conducted applied research

characterizing reproducibility of liver NPS systems for toxicity, metabolism, drug accumulation, and in the Center for Food Safety and Nutrition, they've also evaluated liver NPS systems for their Regulatory Toxicology Program.

Our work has looked at reproducibility, similar results between test sites, similar results within a site if you're using different batches of cells and quality control criteria for cells.

This type of detailed work that is not the type of research that's going to get you a *Science* or *Nature* publication is arguably just as impactful or more impactful as this is what we need to do to be able to advance these technologies to be used around the world for regulatory use in developing products.

Alternative methods data has been used to support regulatory decision-making. We discussed some examples earlier. I'm now going to highlight a couple additional recent examples.

With regard to liver safety, there was a new drug being developed where other drugs class had been discontinued from clinical development due to liver

toxicity.

There was some liver enzyme elevations in rat studies at high doses. When complex in vitro models with 3-D spheroids combined with in silico modeling reproduced the observed liver toxicity of other drugs and suggested that the new drug had significantly reduced risk of liver toxicity.

This contributed to the liver toxicity assessment as described in the new drug application toxicology review by FDA and there's a link to those documents here.

With regard to efficacy and evidence of effectiveness, we have a very recent example where the circumstances are that certain fentanyl derivatives, such as carfentanil, had extremely high potency at the opioid receptor and had potential to be used as chemical weapons.

The Department of Defense supported the development of a high-dose naloxone auto-injector to counter this and instead of an animal model-based approach to demonstrate effectiveness, FDA recommended a model-based approach with in vitro methods feeding

into an in silico or computer quantitative systems pharmacology model, and the FDA-developed model was used to support approval. This is the indication for this high-dose auto-injector that was just approved a few months ago.

Finally, we're going to summarize and discuss next steps.

At the beginning of the talk we discussed FDA's mission and how it's to protect and advance public health with responsibility for regulating diverse products.

We need to ensure the safety, efficacy, and quality of FDA-regulated products and animal studies have played a critical role.

At FDA, we also have a longstanding commitment to the three Rs with successes to date and we discussed some of those examples: harmonization internationally, collaboration with our partners, and introducing and accepting alternative methods for specific context of use.

Newer technologies hold substantial promise. However, multiple steps are required to translate these

technologies into regulatory use while we maintain the same standard of safety, efficacy, and quality of FDA-regulated product areas.

The goal of our proposed New Alternative Methods Program is to spur the adoption of new alternative methods for regulatory use that can address the three Rs and improve predictivity of non-clinical testing.

We cannot develop and implement alternative methods alone. So through this initiative, we'll focus on expanding qualification processes, policy, and guidance to streamline qualification implementation, and then filling information gaps with applied research.

We discussed case studies highlighting components of this FDA New Alternative Methods Program in the cardiac safety space and developmental reproductive toxicity, and we discussed the critical role for collaborations with public/private partnerships with our federal partners and international harmonization of regulatory guidances and guidelines.

There are different considerations for different FDA product areas and we regulate diverse product areas. At the same time, there are opportunities for synergies within the agency.

We discussed how alternative methods in the lung and liver space can have potential context of use across multiple product areas, and there's a potential role for general considerations guidances for specific types of alternative methods.

As I discussed at the beginning, FDA plans to seek input from the Science Board on how the agency can enhance its existing approaches to support the development, qualification, and implementation of alternative methods for regulatory use that can address the three Rs and improve predictivity of non-clinical testing.

While our presentation today outlined FDA's proposed plan, we are interested in additional perspective from the FDA Science Board. We are not seeking specific detailed feedback from the Board today, but we plan to charge a Science Board subcommittee to work on this topic and the subcommittee

report would be presented at a future Science Board meeting.

I'd like to thank all of the FDA working group members that I recognized on the second slide of the presentation.

I'd like to thank the FDA Science Board for joining us today, listening to this introduction and hopefully working with us more on this topic, and now would like to open it up for questions.

Thank you very much.

DR. KOWALCYK: Thank you.

In the time we have, I think it's a good idea to provide some cursory feedback to the agency as they requested.

I think it's obvious that the Science Board will need to devote more time to this issue than we have today. So I concur that a subcommittee would be the best method to study this matter further. We will get started on that process following today's meeting.

I welcome high-level thoughts from the Science Board at this time. Please raise your hand if you would like to provide some feedback.

I call on Ted. Ted, please unmute yourself. Thank you.

DR. REISS: Yeah. There we go. Thank you. Thank you, Barbara.

So I just really have a question and that's can you give us just some insight? Obviously there's -- you're doing tremendous work. There's a lot going on moving in the right direction in very difficult areas, as Janet had outlined at the very beginning, and a critical one.

Right now, does the agency -- you started by talking about a lot of collaborative groups, but how does the agency prioritize what they're going to work on, what they're going to spend their time, energy, and resources on in this particular area? Can you give us just some general thoughts or insights to that?

DR. STRAUSS: I can provide a couple comments.

I don't think there's one answer to that question, and work today has been prioritized within the different centers at FDA and the centers best know the products they regulate and the questions and needs

at hand.

With this new initiative, we have a goal to bring up coordination of major efforts to the Office of the Chief Scientist within the Office of the Commissioner and be able to even further coordinate, prioritize areas.

We're interested in feedback, external feedback that will include from the Science Board, from other external partners, and it's a continuous process, and we get feedback from the reviewers in the different Product Centers where there's opportunity.

So there are many answers to that and we're hoping to coordinate those activities better at the agency level.

DR. WOODCOCK: Yeah. And I would add it's been partly entrepreneurial I would say up till now. Where there was a huge need, there was a champion, for example, in cardiac safety and there were available technologies that could be put forward. People ran with them.

DR. KOWALCYK: Okay. Thank you.

Dr. Nolan.

DR. NOLAN: Thank you.

I'm very excited about what you're talking about, especially being a veterinarian and in a profession devoted to animal health and welfare, and, you know, it just strikes me as an academician we have lots of people that would love to partner with you on this kind of work. It just seems right for a big grant push, right, extramurally-funded program to get us going and working with you. So well done.

DR. WOODCOCK: Yes, this is Janet Woodcock. I agree that would be very desirable. We don't have the funding for that currently, but as David said, we are seeking funding. Much of it would be to set up our internal program, but to be able to help spur this translational research, some more dollars toward this effort would be helpful.

What do you think, David?

DR. STRAUSS: Yes, I would certainly agree.

DR. KOWALCYK: As a follow-up question, have you reached out to the research funding agencies to make them aware of your priorities?

DR. STRAUSS: Yeah. We actively, you know,

collaborate with many of our federal partners. We've had longstanding collaborations with NIH and other partners, such as in the micro-physiological systems space, and we're continually working with those partners to look how we can synergize our efforts.

DR. KOWALCYK: Okay. Thank you.

I'll now call on Dr. Afshari.

DR. AFSHARI: Yes, thank you.

This is Cynthia Afshari. Dr. Strauss, thank you for your presentation. I mean, it was a superb kind of compilation of a lot of literature and actions by the agency and so it's going to be a really, I think, nice reference source for everybody listening in and beyond.

You know, I will say again, you know, three Rs is really important to all of us and so I think through the years we've seen that the science wasn't necessarily always ready and I feel like, you know, at this time where we see the advances coming and various analytical methods, cell biology methods, also our knowledge of systems biology not only from preclinical models but also now more from human really does make

this the right time to kind of put the muscle behind it to push some things forward.

I like Dr. Reiss's comment around collaboration because I think there are definitely, you know, other government agencies, private industry, and others who really could come to the table together and it's not just in the methods development but we all know there's a lot of considerable expense and energy it takes to qualify these and so I think just again this subcommittee idea is a great one to think about some of the aspects of how we collate the infrastructure that would support those programs in terms of, you know, control sets, test sets, how we transparently share methods to understand how we can standardize faster is something that's -- you kind of feel like maybe it's not as long-hanging fruit as I'm saying, but that the time is now for that.

So hats off to you and the agency for kicking this off here today.

DR. KOWALCYK: Dr. Strauss, you're on mute if you're trying to respond.

DR. STRAUSS: Yes, sorry, I was on mute and

then I muted myself.

Yeah, no. Thank you and we hope you can join us on the subcommittee potentially.

DR. AFSHARI: Absolutely. Thank you.

DR. KOWALCYK: Are there any other comments or questions from the Science Board members?

DR. BAHINSKI: Barbara, I think I had my hand up and I don't know if you see it. This is Tony.

DR. KOWALCYK: Oh, go ahead.

DR. BAHINSKI: Yeah. Really fantastic overview by Dr. Strauss. Thank you very much.

Maybe just a comment. I mean, I've been lucky enough to be involved with some of these efforts over the last 12 years and just, you know, some history.

The FDA's been intimately involved with this since 2010 when they had the first collaboration through the Collins Fund with the NIH for developing a heart-lung micro machine and then through the FDA and DARPA/NCATS efforts with the tissue chips from 2012 on through, you know, the BAAs. So it's really, you know, been fantastic and they've been a great resource to a

lot of these and I can see them really implementing these going forward, you know, great source of guidance for a lot of folks.

Maybe, Dr. Strauss, a question to you. I know that there's an Alternative Methods Working Group right now that, you know, helps identify these across the FDA, all the different divisions. Maybe you could speak a little bit to some of the efforts that they're working on right now and also I know that with stakeholders, you know, collaborating with those.

I know the IQ Consortium, NPS Consortium has been very helpful in working with the FDA. Maybe you can give a little more insight and background on some of those collaborations, also. I think that would be useful.

Thank you.

DR. STRAUSS: Sure. I'll try and do it very briefly. I know we don't have too much time.

One of the earlier slides in my deck had different FDA reports, including Advancing Alternative Methodologies at FDA report, and there was a link there to the FDA Alternative Methods website which I would

refer people to for more information in that report about the Alternative Methods Working Group.

Your second question, I'm sorry, can you repeat that?

DR. BAHINSKI: It was just around stakeholders input, you know, and users, people like the IQ --

DR. STRAUSS: Oh, yes.

DR. BAHINSKI: -- and NPS, yes.

DR. STRAUSS: Yeah, no. The IQ Consortia, which is the Innovative and Quality Consortia related to drug development, they have put out an excellent set of papers that describe considerations and potential validation approaches for many different organ systems, for micro-physiologic systems.

We engage with that group and that kind of engagement with that group represents the scientists in industry that would be the users of these technologies and it's critical to have interactions with them, with the developers of the alternative methods, and, you know, that includes academic sites and people working with doing research in academia, with companies that

are developing these methods, and, yeah, it's very important to bring these different stakeholders together, and we have done that.

I discussed a few examples and we need to continue to do that to advance these new alternative methods forward.

DR. WOODCOCK: Well, I mean, this is about dragging some of these over the finish line and as somebody said, we know how hard it is to do that final translational step, to actually figure out predictive value of what you're interested in for humans, and I think one of the things that needs to be done is if we have methods that people agree are standardized and validated as far as their analytic characteristics and their performance, then we need to test them in development programs, encourage the manufacturers to incorporate them in their development programs because some of those development programs will have human read-outs for the toxicity and therefore it's a very unusual situation where you actually get the human read-out for some of these -- you know, you get the human exposure because just comparing to the animal

tests alone is not helpful because you don't know the predictive value of that test really, except through historical means.

So it's a conundrum, but I think this last step is going to require people to be using these in their programs so that we can get data, like real-world evidence, you might call it, of how these actually perform in the context of use for which they're intended before they're actually used for regulatory purposes.

DR. KOWALCYK: Okay. Great. We're running close to time and so, Dr. Sarwal, you have your hand raised.

DR. SARWAL: Yes, I'll be very brief and actually I think a lot of what I was going to say has been addressed very well by my colleagues.

I just wanted to really extend my congratulations again to Dr. Strauss for an outstanding presentation which summarizes something that's incredibly timely.

I just wanted to add the last thing is a subcommittee, I think this is again applaud the FDA for

really taking this path forward. I would just say that the charter for the subcommittee is going to be extremely important for us to, I think, set.

One of the things we actually want to start trying to achieve here, because this was going to be so much that we actually want to achieve, is funding, partnerships, how we're actually going to advance a lot of some of the very rare human diseases that we're not able to even bring better therapeutics to because of small numbers and sample sizes, etcetera.

So again applaud everyone and just say that our work is cut out as what the charter for the subcommittee should be and how we prioritize actually what we do going forward so that we can achieve this and this could be a pretty long subcommittee because there's a lot of work to be done.

DR. STRAUSS: I agree completely.

DR. KOWALCYK: Thank you very much and I agree, as well.

Tony, you still have your hand raised. I don't know if you have another comment or question or if that's from your previous one.

DR. BAHINSKI: Apologies. Previous.

DR. KOWALCYK: No worries.

Okay. So we're running on time which is wonderful.

We are now going to move on to the Commissioner's Update. We're glad that Dr. Califf can join us this morning. We're looking forward to his Updates and Thoughts on the Greatest Challenges the agency faces, his own top priorities and the plans for his term as Commissioner.

I'm sure if time permits, Dr. Califf may be able to take a few of our questions, as well.

Dr. Califf, welcome.

Commissioner's Update and Data Science Efforts

DR. CALIFF: I guess I better ger my video on here.

Hey, everybody. It's good to see the Science Board again in my second time around. I hope there will be time for discussion. Remind me how much time we have on this agenda.

MR. RAGHUWANSHI: We have an hour, Dr. Califf.

DR. CALIFF: All right. Well, an hour's plenty. I got a few other things to worry about today, including the fact that I have two 18-year-olds graduating from high school, one graduated last night and the other is at 1 o'clock this afternoon down here in North Carolina, which is why I'm remote for everything today. So there are some higher priorities than FDA in my life right now, I guess I should say.

So I'm going to bring up some slides and what I'd like to do is spend half an hour on priorities in the call to the science community and the other half an hour specifically on the topic of data science and quantitative disciplines to get your ideas about how you can be helpful or whether you see this as something not necessarily in your arena.

Let me get on the share screen here. Okay. Let's see. Can you see the slides? Okay. Good.

MR. RAGHUWANSHI: Yes, sir.

DR. CALIFF: All right. So like I say, two topics today, and I hope most of the time will be for discussion.

So since this is the Science Board, I've been

asked by Holton Thorpe to write something for science and he actually hoped I would have it submitted before I started. I'm now four months in. A lot's happened in four months, but I think, you know, to me, the message is even stronger than it was before, at least in terms of the way that I think about this.

Basically, you know, there are a list of short-term priorities, things that have to get done, and, you know, I'm happy to answer any questions about those that you want, but because I do think we have a very strong group of center directors who can manage their own business, I think my role is to look beyond the immediate to the needs that we have to put the FDA in the right position for the future.

That's kind of an interesting contrast for me because I just finished a talk to the FDALI, the legal group that focuses on the FDA, and now I've got the Science Board, so trying to make this transition.

I'll note that Dr. Woodcock is giving a very prestigious address to the lawyers tomorrow. She has some pithy things to say. I haven't seen her comments yet, but I'm looking forward to hearing about them.

So as I look at the long term, there are a number of key priorities. I'm writing a sort of sister article for *JAMA* for the clinical audience, but I'll just go down this list and then open for anything you want to ask about until 10:30. Then I want to talk about data science and quantitative disciplines and get your ideas there.

I think no matter what, the work of the FDA relies on a workforce that needs to be talent deep in science and related disciplines, in addition to the group I just came from, many lawyers at the FDA for good reason, and, of course, the public health policy discipline.

You know, I hope the science community will get more proactive in interacting with the FDA, both to support current employees but also consider a term working in the FDA.

I think the scientists who are really interested in translation, the best thing I could think of to do would be to spend a few years at the FDA seeing how things actually do get translated and then, you know, either staying or moving on into the field

with a much better knowledge.

Also, I think it's still the case that the understanding of how all this works is pretty meager in the academic community and we would be well served if we thought of better and better ways to have more people aware of the issues that are involved in translation.

Obviously the COVID pandemic response is a huge issue. My general view of that is the science community has magnificently risen to the challenge and so here we are with we have a COVID hearing on Thursday with the Senate and I think we can proudly say we have vaccines that work, treatments that work, diagnostic tests that work and that are now in your home.

We have one big problem which I'll get to at the end, but I think it's obvious that we're going to have to continue this adaptive approach and maintain the intensity because the virus is not holding still. It's continuing to evolve in ways that we're going to have to respond to.

There are issues in preparing for future pandemics in a time of climate change and that are

going to require the best of science.

I feel like substance use disorder and overdose, this is the opposite of what I'd say about the pandemic, I think the science community has been pathetic in this regard and needs to pay a lot more attention to it. It is just not a sexy thing to do to study pain and its treatment or to focus on drug overdose, but we had over a 100,000 Americans die last year of drug overdose. We have huge amounts of synthetic fentanyl and methamphetamines being mail ordered into the United States.

None of you, I'll bet, have 18-year-old grandchildren like me but many of you probably have children and we have children dying on what they think is recreational oxycodone that's fentanyl-laced product dying on the first dose.

We need different treatments for pain. I don't think -- in my view, this is not going well, and the FDA obviously is not in the business of developing treatments. Our goal is to facilitate the development of treatment, but we don't have a National Institute of Pain. There's not a specific funding agency and while

some efforts, you know, it's better than it was, we've got a long way to go.

Cancer, I would put back in the pandemic response category, it's been basically a love fest of science and medicine and the recent findings in color cancer really validate that. So this is a very top priority for the President. It's a great time to be in cancer biology, working in the translation of cancer therapeutics. I'm all for it. Let's keep going.

Gene therapy is an area that sort of lulled a little bit during the pandemic but the science didn't lull and I think we're going to see an explosion of attempts to translate gene modification and other types of gene therapy in the practice for rare disease and also for common chronic disease to some extent.

But we don't have a system in this country that's good at measuring something beyond the acute effect and, of course, what's characteristic of these treatments is that they're going to be very expensive upfront with hopefully a lifetime of benefit, but we have no way of ensuring that there are not long-term toxicities and other effects that we just can't

anticipate right now.

So we need a scientific commitment to both the exciting front end of the biology and the very important back end of what happens afterwards which I think also involves multidimensional biology but also clinical research.

On common chronic disease, we just passed a negative milestone. The average American is expected to live five years shorter than the average person in other economically-developed countries. I want to say that again. Five years shorter.

So despite all of our prowess, all of our innovation, we have worse health outcomes than any other high-income country and we're moving in a negative direction, not a positive direction.

The cause of this is not mysterious in terms of the diseases. It's the common chronic diseases that we all know, heart disease, lung disease, kidney disease, mental health issues with suicide, and gun violence.

We've got to pick up the pace here on common chronic disease and I think for a whole variety of

reasons this has not been the focus of the science community at this point.

Tobacco is right there with drug overdose. We have a number of -- you'll hear a lot of press about tobacco but 500,000 Americans will die of tobacco-related illness this year, and we need the science community to get more engaged to figure out what to do.

I don't know if Janet's still on, but the sort of in joke within us is that we need a center for vices and bad decisions, but there are a whole set of things like tobacco and opioids where our society has decided we're not going to completely get rid of them.

The issue is what's the right amount of regulation to reduce the harm to a minimum, given that they're going to be around, and you could add Kratom and cannabis products to that, which I know you're going to talk about. So I look forward to the outcome of that discussion.

The next area is digital transformation. I don't need to tell any of you that we're in this era. I'll talk more about that in the second half hour, and then food has obviously taken up much more of my time

than I expected, but the science in food is, I would say, even more exciting than the science in medicine.

If you look at what's happening to the food supply in the face of climate change, the need to understand what good nutrition is, the availability of big data now, of quantitative methods that can measure population outcomes much more effectively, and global digital technology to look at things like water inflow and the plots of agricultural territory and understanding how to grow crops most effectively for the highest nutrition.

Then the thing I was saying about the pandemic response, the big thing that we're losing on is misinformation. I've been focused on this for a decade. My five years at Alphabet, I learned more than I ever hoped to know about misinformation and what I say is there's no robust academic enterprise in understanding what misinformation is, how it's transmitted, how it proliferates.

I can't find a single person that has what they would even claim would be a viable proposal for what to do about it.

There are elements that we know we need to do, but a winning strategy is yet to be found. We need the science community to wake up and it ought to be the job of every person in the science community, in my opinion, to spend some part of everyday doing something about misinformation. It's eroding trust in our organizations and in science itself, and, you know, we have living proof in the pandemic or I shouldn't say living proof, hundreds of thousands of people are dead for no good reason other than they were persuaded not to get vaccinated and didn't get access to antivirals that are highly effective.

Then last I'll mention One Health and Globalization. Obviously we're living in a coating of bacteria and viruses that are common to us and the animal kingdom around the world. If ever there was a place for high science and big data, this is it, and, you know, I think the science community needs to rise to this challenge. It's quite a daunting challenge.

So I'll stop there and happy to answer. Why don't we go to 10:35, gives us 10 minutes for any questions that you might have about this part?

DR. KOWALCYK: Thank you, Dr. Califf.

If any Science Board members have any comments or questions, please raise your hand. In the meantime, I do have a question.

Of course, my background is in food safety and I noticed that food safety wasn't one of the priorities in the food category which surprised me a little bit given the crossover between food safety and infectious disease as well as two ongoing outbreaks that have commanded a lot of attention, one in baby formula involving Cronobacter and the other one that involves peanut butter.

Could you comment on your priorities around food safety?

DR. CALIFF: Yeah. I'm sorry. That's an omission in our slide put together in a manuscript that's in progress but there's a big section on food safety.

So, you know, I mean, of course, you know, that's a priority and it is an area of high science. I mean, I think the genome sequencing is a good example of where it's made an enormous difference, but there

are other areas, like the use of social media to figure out where outbreaks are coming from when they occur.

So I'd be crazy not to say it's a priority. I'm spending more than a couple hours a day on food safety as we speak. So we do need the science community to be more involved in helping out to develop these methods where technologically I think you'd probably agree with me we have the capability of having a vastly different and improved food safety system.

DR. KOWALCYK: Yes, I would, and since I don't see any other hands raised at the moment, I'll just follow on to my comment.

You know, I was happy to see that One Health and surveillance are on your list because those are really important when you're talking about infectious diseases, and, of course, one of the challenges we have in our public health surveillance systems in the United States is that they have not been updated in a number of years and sometimes lack of capacity which goes to the workforce development priorities that you noted earlier.

For example, many of the local public health

agencies that are charged with surveillance of foodborne diseases and other infectious diseases were also charged with COVID pandemic response and had to stop doing a lot of their surveillance activities during the pandemic and so it's important that we build our capacity in that area because of infectious diseases certainly not going away.

DR. CALIFF: Well, I think you're right on several key points here. I've got absolutely no argument with what you said and you briefly referred to something which I think is really, really a complicated problem when you have constrained resources, where do you allocate them.

In the area of food safety, in particular, I had a fascinating meeting yesterday with Steve Troxler, the Agricultural Commissioner for the State of North Carolina. He's like the dean of agricultural commissioners now because he's been re-elected 10 times. I think he has to run for office every two years or something. So he's been around and this came up with infant formula. What do you do when you'd like to have optimal safety but basically if people can't

eat, you know, that's a balance that's going to have to be reached while you fix a problem that you discovered?

Just to make sure everybody's awake, his prediction was we're going to see a lot of that over the next year because of the impact of the Ukraine, in addition to the fact that our supply chains in the U.S. are tenuous right now, and so, you know, I would much prefer to make those trade-offs based on quantitative information that enables us to assess risk as opposed to just somebody's best guess.

I think that's a very high form of science. I think of it much like the way we think about data monitoring committees for clinical trials. When you see a trend, when do you say it's enough to do something and how do you balance the need to get answers versus the risk to patients who are participating?

In this case, there's a lot more at stake because interruptions of food supplies can cause enormous problems.

DR. KOWALCYK: Yeah. I would agree with that. Of course, in the food safety community, we

often say that it's not food if it's not safe and so, of course, the intersection between food safety and nutrition and food security is something that really needs to be prioritized and, of course, we're moving in that direction in the international arena.

I don't want to monopolize the time, but does anyone else on the Science Board have a comment? Ted?

DR. REISS: Yeah. So Ted Reiss here, Commissioner. Thank you for your comments this morning.

So I also share your thoughts about innovation, the drug development process. The regulatory side is not as well understood outside of the small development community as it should in the academic community and so on and so forth.

I think, you know, NCATS, the CTSA is supposed to help with that. I think they've made some inroads, but what would your thoughts for next steps sort of be, and how do you see the FDA helping to promote that knowledge going forward?

DR. CALIFF: Well, I think of it as a multi-dimensional issue that requires -- you know, it's a

dance with two partners or more, but the FDA part of it is, you know, the sourcing program, I think, is a good start, but it's limited to certain institutions.

I think we need to promote educational programs and participate in them with curricula that reflect less about -- well, let's just say has the basics of the things that you need to know about how the FDA operates but also reflects the magic of innovation and product development which I actually think that's very hard to teach. It's best done through examples, but just knowing, you know, what the rules are doesn't get you to where you need to be in terms of understanding translation.

I mean, this thing that I was talking with the lawyers about today which I think Janet had a particular way of saying it that got my attention back in 2015, FDA can create an entire industry with one rule.

What we need to do, you know, regulation can actually improve innovation if it's orienting people towards things that will work as opposed to, for example, chasing biomarkers which aren't truly

surrogates as a therapeutic target would be one that throughout my whole career has been a problem and it still misunderstood, I think, by a lot of people who are more in the basic science community.

So but ultimately part of what I'm trying to do once we get formula on the shelves, which, you know, is the Number 1 priority of the agency right now, we need to call out people who are outside the FDA to activate on certain areas where they can make a difference because this vast universe of information out there is way bigger than we can handle on our own.

DR. REISS: Yeah. Great. Thank you.

DR. KOWALCYK: There's time for maybe one more comment from the Board.

DR. CALIFF: If no one else has an area that you think should be a priority for the science community that I haven't named, thanks for catching food safety. I need to get that on the table before I submit it.

DR. KOWALCYK: You're welcome.

Well, back to you, Dr. Califf.

DR. CALIFF: Okay. So I want to try to get

some of your thoughts about the quantitative community in data science. I only have preliminary thoughts. I've talked with all the center directors and gotten some input from them. I've talked with people around the agency to some extent.

So ultimately I want this to lead to a question of whether there's something the Science Board can help us think this through or I'd welcome your disagreement with the way I'm thinking about this.

So a big part of my background, you know, in terms of crystallizing my thinking came through work that was done with a number of organizations on the 4th Industrial Revolution and just to remind you of what the Industrial Revolutions were, the first was water and steam power to mechanize production.

The second was electric power to create mass production and, of course, the entire society changed with each of these revolutions because these elements were central to commerce and human interaction.

The third, which we're sort of on the tail end of now, was electronics and information technology to automate production. That's very far along, and as

I've gotten back into the food world, it's really amazing to see the extent to which automation is critical not just to the supply chain but to farming itself and Steve Troxler yesterday said if a farmer doesn't have access to broadband internet, that farmer's not going to be competitive.

So I think we're pretty much there on the 3rd Industrial Revolution, but the 4th is what we're on the front edge of now, the fusion of technologies. The boundaries are blurred because we're all moving to a digital world and I don't know about you.

I worked at Google until a few months ago, but I found myself intrigued by the engineer who's now declared that the latest Google AI is Sentient which I hope is not the case but who knows. I don't really have an opinion on that.

But what I do know is that increasingly as we look at our various areas of science, they are looking more and more similar rather than different because ultimately the sort of basic element of science is the digitization of the relevant information and it's leading to possibilities that were just unheard of

until now.

An element of this is something the National Science Foundation has been working on for awhile, convergence, which you're all familiar with, but something which I know there's a great appetite for within the FDA but which is not necessarily engendered by this structure that we currently have.

Let me be clear I'm not arguing for change in structure today, but I am hoping to have more thought about how to account for where science is going as we look at the future of FDA as it relates to society.

At a more basic level, I would just point out it's very clear to me in my first four months back the amount of heat generated by an FDA decision is inversely proportional to the quality of the evidence. The FDA functions well when it has high-quality data with appropriate methods applied to derive a conclusion and one can argue about the meaning of the conclusion.

For example, should tobacco products be banned because tobacco kills people and there's no redeeming health benefit, but others would argue, well, people like to smoke tobacco. So that has to be

considered. That's not the science part of it, but when the science is known about an individual product, the arguments are much less intense and severe.

Now I borrowed this slide from Steve Steinhoople, who's an old colleague. He was a chemical engineer at Kodak and one of his jobs was to defend the patents for chemical processing of film way back in the good old days of photography and you all know the story of what happened there when other companies moved to digital photography. Kodak was in big trouble because it continued to bank on chemical processing and the industries that basically are last to move to digitization are the ones that we deal with at FDA, particularly health care delivery and the medical products industry which has had a lot of trouble making the transition in a way that makes things more efficient for the consumer.

The cost of health care keeps going up, the cost of drugs and devices keeps going up, despite the fact that information technology is part and parcel of what's done. The transformation hasn't yet occurred.

So I would argue that FDA's role in helping

to make the transformation, like other industries where you have more effective products at a lower cost, is something we ought to be thinking about.

But it's also true that we can't just do this based on a theory of digitization. We have to have high-quality data and it's just emphasized by this slide which I've used a lot and explains a lot of the problems that we have when industries make claims in the absence of high-quality evidence.

Part of this effort and part of the global change that's occurring does have to do with sharing information and one of the ramifications of this in my opinion is that a lot of the information that's relevant to medical products or agriculture or cosmetics or food supplements is increasingly going to come from sources outside of the industry that makes the product and the FDA.

That is, in the real world, as things are more and more digitized, there's going to be more and more data that we are going to need within the FDA to understand and contend with to fulfill our mission and that data is going to increasingly be shared.

Now I'm not going to dwell on any one of these slides but just for fun, I sort of, based on what's happened in the last four months, I would say there's a vast need at the FDA for integrative data science, including all the quantitative sciences.

So just center by center, you'll notice that Items 1 and 2 for each center are the supply chain. The supply chain in agriculture and medicine is considered proprietary and confidential information for each company. There is no ability to combine the information and while it's increasingly digitized within each company, it's not shared with any federal agency and so we don't have a system to anticipate, preempt supply chain problems.

The second one in every slide is optimizing the system for inspections, investigations, and system quality. It's different for each agency what the principles are to some extent, but basically we need to move from the old system which is in process, but I think we need to accelerate the use of predictive algorithms in helping us go to the right places at the right time and understand the information that we're

seeing about these vast industries that we're regulating.

You can see the others here. I could talk about each of these in a lot of detail at this point, but I won't bore you with it.

For CDER, we're just going to see a lot more real-world evidence and I think a good example that's recently happened, Paxlovid is a highly-effective antiviral for COVID, and then some prominent scientists had what's been called Paxlovid rebound. Turns out there's a similar phenomenon that happens in placebo groups but that didn't stop it from being contagious viral Twitterati-driven perspective that maybe we need to rethink Paxlovid and there's nothing wrong with that. The issue needed to be addressed.

My main point is this happened totally beyond the ability of FDA and Pfizer to get ahead of it because it was very quick and driven over the internet and we are catching up now. There's a paper today about it which I think will be helpful. But there are many, many more examples like this.

For CFER, gene modification and vaccine

safety are just big issues. I got an amazing 20-page single-spaced document from the anti-vaxx community yesterday that has plots that look every bit as credible as the best science that you'll see and we've got to be able to integrate all the various sources of knowledge as best we can in the post-market phase for the public health, not in the interest of any individual product but for the public health.

And then devices, all you got to do is think about devices laden with software to realize that we're in the digital era and there are many issues that we need to address to deal with the information that's going to be derived from these data, most of which are not being used.

In my world as a cardiologist, the amount of information available when a person has a pacemaker or an ICD is just amazing, but we're only taking advantage of a fraction of that to improve health, and then we've already talked about One Health.

I think CBM is the most underappreciated part of the FDA and it's going to play an increasingly critical role but very dependent on data science.

Now in my career, I've been in multiple organizations that struggle with the question of what is data science and I would just say everybody has a different definition.

I happen to like this one which basically says there's a big table called Data Science and around it sit all types of quantitatively-oriented professionals and depending on the question at hand, they need to be able to work together as a team because no one person can be an expert in all of these different disciplines.

Little did I know that during the five years I was away, Janet and Amy Abernathy recruited a couple of key people into the central organization who had put together something called Data Forward which is, I think, a good start to bringing things together and they basically advertised that they were here to help in the area of data science and they had some introductory sessions to which over 1,400 people subscribed. So that's just telling you, no surprise, we got a lot of people who are involved in one part or another of data science representing all the centers

and you can see, like all of us, many felt confused about data science before the sessions. Afterwards, look at that, 99 percent excited, less intimidated, interested in learning more about data science.

In the dream world of Bev and Rahm, our two central leaders, we would go from an FDA which is disaggregated, dispersed, fragmented, disconnected, full of really good people, to one which is a functional ecosystem hiring the best people, always making sure the best methods are applied.

This is something I have observed at every organization I've been in, including Google. Often the analysis is given to the person who is within the subunit in which the work is being done without awareness there may be a world's expert sitting next door in a different subunit that just as a consult could make a big difference in how the problem was approached.

The system made the point. A lot of work was put into thinking about what are the skills that you need on this team and detailed definitions were developed in a way as sort of classifying people in how

they might self-assess for their skills across this breadth of things you would want to know about data science and quantitative disciplines.

As good people would do at the FDA, a lot of people did their self-assessment and the good news is we got experts in all of it. The bad news is they're disaggregated and often off in corners of the FDA universe and other people may not know about them.'

This is a slide that I thought was most amazing. Even with a cursory effort, it was identifiable that there were more than 60 active data communities within the FDA, groups of self-affinity who hang out together to some extent to share methods and knowledge and ways of doing their work.

One has to wonder maybe this is fine. It shows that people do want to hang together when they have a common interest but maybe with a little more central support, this could go even better.

Each of the centers has responded with its own view and I can tell you the organization of the centers has some common elements but a lot that are different.

This is just a look to give you an idea of the scope of this within the FDA. This is CDER which is our biggest center, as you all know. You look at the strategic programs, over a hundred people who are quantitative in one way or another. Translational science is over 400 people, surveillance and epidemiology, 93 people and counting, contractors. So a lot of people representing just about all the disciplines that I would have listed who need to be around the table.

You know, it's very highly organized so that within the basic function of the FDA, the required function of FDA, there is an organization where people are accountable for the tasks that they are supposed to do and I'm not arguing that and I have no reason to want to have anything to do with that sort of organization because I think it works pretty darn well. People do review applications and handle inspections and all of that.

My question is can we supercharge the system by creating a better interstitial environment across all these entities so it leads to the up-scaling to the

best level possible and bringing the best talent to the problem wherever it may be?

So I'll close with a couple of just slides from my experience. In doing this, I don't intend to differentiate whether one group is better than another or more superior. I've seen that in academia. I've seen it in industry. What we need to do, you know, I'm a basketball aficionado, we have guards, forwards, centers, team managers, coaches, general managers, I don't think any of them are better than the other. They function as a team and when the team doesn't function, the team loses and so I would hope for the same thing here.

But I do think, I'm pleased to say my granddaughter has graduated from high school today, it's claimed she wants to be a statistician and that's what she's going to major in and I told her you got it made if you love statistics because there is a massive shortage already and there's going to be an even greater shortage because we all know that we need people who cannot only do quantitative things but can translate those quantitative things into words that

people can understand.

So I'll stop there and I'm interested in your feedback on this thinking. I'm purposefully not suggesting any particular structure or any particular change in function, but based on my experience with the Science Board in 2016, I just have a hope that you all, since you represent different disciplines and different places, that you might be able to help us out.

DR. KOWALCYK: Thank you, Dr. Califf, and we'll again open it up for some feedback and comments from the FDA Science Board. While waiting for people to raise their hands, I can go ahead.

I'm a statistician by training, an epidemiologist. So this is a topic very near and dear to my heart, and so I think that this is very important work. I think a lot of organizations, like you pointed out, are struggling with this and FDA in particular, I'm most familiar with some of the efforts going around in food safety to integrate data, leverage existing data sources, and improve workforce capacity.

I think from my perspective, that's one of the biggest things we need and you mentioned it. We

need translators. I completely agree. You can have data scientists and statisticians, but if they can't translate into the language of the traditional scientists, it's going to be very difficult.

I think the biggest challenge we face in academia is developing a new generation of data scientists who both understand the statistical methods as well as understanding the area content.

So I will now -- Dr. Sarwal, you have your hand raised.

DR. SARWAL: Yes, thank you again. Fabulous presentation, and I think such an unmet need from all of us and so I have a background also in biostatistics and bioinformatics, and I think it is key for us moving forward, especially as we're trying to develop more hypothesis generation for disease mechanisms rather than using, you know, peer literature for just revalidation of perhaps biology that we all believe maybe has significantly greater heterogeneity in understanding disease than we may have appreciated maybe a decade ago.

So I think I totally echo all the importance

that you have highlighted here.

As a user and somebody that actually runs groups here, I think you've highlighted a very important challenge is the fact that the person that runs the numbers very often does not understand the biological concepts.

We have been able to work very successfully through that with a very close interface of both sides because it's very hard to actually get a single person have both aspects actually -- I mean, both, I think, skills sets being brought in.

I think, as you showed, there are different departments at the FDA. I would like to kind of maybe understand more how that kind of assimilation can occur at the ground level because I think that's going to be critical for us to create almost these kind of multi-disciplinary partnership teams and have content area experts for diseases to be teamed up and to have at least some basic statistical understanding so they can work with that data scientist and so really I think thinking about doing science with a new model because we don't usually fund labs with a synergistic team

model in place but I think the future is really going to require that and so I would be interested in your, you know, thoughts on that.

And then the second is I'd like to again -- and I think you touched on this but the trove of data that exists in the public domain and the ability to actually develop some kind of systemized format of how the data which exists in very different dimensionality and different datasets using different platforms, in different, you know, methods of estimation, like even if you look at transcriptional platforms that are present that at various kind of different probes and different mechanisms, etcetera, but there is a way to unify all of that data and to get it normalized to actually allow us to create maybe very large hypothesis-generating tests with validating occurring within the lab through these kind of synergistic data scientists and, you know, basic kind of people that actually understand the molecular biology, kind of those partnerships things.

So I would be interested really in, I think, FDA's thoughts on creating these kind of new ways to

handle this kind of data and how you're thinking about it, too.

DR. CALIFF: Let me first say the first two comments are music to my ears and I hope I'm going to convince you to work with us over a period of time because I don't see this as, you know, file a report and then everything happens.

This is to me like a core to be able to work on. I think you're probably aware that my career, I'm not a data scientist, my career was built being the clinical side. You talked about the biology side with the data science.

There's an equal issue on the clinical side with the data science and so I feel like understanding the issue quite well and I think it is a very rare person who can master all sides of that equation and so we need teams and I do believe the FDA is fundamentally in the Review Divisions built on teams.

I'm just saying because of what you brought up both in the biological arena and I'm sorry I missed the last hour by listening to the very end of it, but I look forward to getting caught up on it, in the

biological area and in the product life cycle arena, the amount of data sitting outside the companies and outside the FDA is just growing and growing.

I probably don't need to tell any of you that working at Google, I was amazed at the amount of publicly-available information that if you have smart people, which I guess you could say we have a lot of smart people, it's very ascertainable but does require a huge amount of effort to normalize or organize the data in a way where the different dimensions fall into place.

There again, you can't even do that without someone who knows the topic to figure out if it makes sense. I did have quite a few engineers who told me things like high blood sugar predicts diabetes. Okay. Well, that's nice to know, but I'd also point out in the clinical arena, there's something that worries me a lot that I saw full force from both sides.

There is a lot of data about medical products and interventions that sits outside of the regulated domain in the hands of consultants who work with health systems and do analyses with no transparency to the

public that drive decision-making about which products go in formularies and get used and to me that's just a harbinger of the future if we don't get organized to deal with it.

` So to go back to the fundamental issue, I think what I'm asking for is help both inside and outside the FDA, thinking through how to configure teams to take on this added dimension of science which is now possible.

I have some starting ideas, but the FDA also has to review products and do surveillance and that's what it gets paid to do, and so I don't want to -- because it's interesting science, I don't want to do anything that detracts from the fundamental mission. I want to add to it.

DR. KOWALCYK: Ted, you have your hand raised.

DR. REISS: Yeah. I just want to make a comment because -- well, just a couple of comments, just throw it out, see if anybody wants to comment on my comment.

Obviously, you know, Rob, I think what you're

proposing here is four plus critical not only for the FDA but for development, innovation, the academic community, and so on and so forth.

There's lots of -- as you were pointing out and others, there's lots of technical issues here. You're combining data, having the right training, so on and so forth, but in my mind, also, having spent most of my career in pharma that requires integration of knowledge and so on and so forth to be successful is that the fundamental -- one of the fundamental issues that can't be sort of lost in all of the technical aspects of this is the cultural aspect of collaboration and working together on interdependently.

You know, without sufficient attention to sort of changing so that the mindset and the culture so that people think first to work in this way rather than within their silos, you know, sharp elbows, get away from my RO1, these sorts of things, you know, that either this will progress slowly, you know, as we're sort of seeing over time, or, you know, we'll have major challenges.

But I just wanted to throw out sort of that

issue about the cultural change that has to go hand in hand with these technical issues.

DR. CALIFF: No argument from me. I mean, it's interesting. I won't name any particular pharma organizations, but there are wars going on right now between statistics and data science in several large pharma companies that I saw last year and I think what I'm hoping is that there will be some, I call it, interstitial structure that supports collaboration to help the culture change because there's a reason we have separate regulations on clearance of devices and approval of drugs, for example. They can't be just merged and shouldn't be, I don't think. Thanks.

DR. KOWALCYK: Great. Dr. Afshari, you have your hand raised.

DR. AFSHARI: This is Cynthia Afshari. Thank you for this and, you know, I think you laid it out nicely, the challenge and the opportunity here of data science.

You know, in terms of advice or experience, you know, some of my comments are similar to what we just heard from Dr. Reiss, but one of the pieces of

advice I guess I would say and that I think is not truly inherent already in the FDA teams that, for example, review drug products is the diversity of teams and, you know, you have the quantitative computational statistics side, but when you say biology, we recognize biology as a host of disciplines and so the power really comes in terms of bringing those groups together and so I think we have to think in a way of, you know, it can't be an us and them and we also have to guard against what could quickly become group think.

So maybe an example you talked about, you know, you get a certain group together and you're like, well, let's correlate with diabetes. You know, I'm thinking about an example where you could see, for example, maybe AEs related to a certain target organ and you look at expression of that target and you say aha, there's a link here, but then there's another aspect of, well, if it's a nuclear target and you're drugging it with a biologic that's going to hit the membrane, the chance of that, you know, being the cause is probably, you know, very low probability and so that's where you can imagine you're bringing together

biochemists or cell biologists with pathologists, with physicians, you know, in addition to the quantitative pieces and so, you know, that's a must do in my view and I think FDA and the drug review teams are very diverse by nature.

So I think as we carry this into looking at broader datasets, we have to make sure that the individual voices come together in a culture dynamic of a team because in my experience what happens is sometimes, you know, let's just say the biologist side is sitting on one side and they're getting an output from the data science teams that’s already reduced in dimension and, you know, maybe shining the spotlight in a simple way to an association but without those other pieces, you would come to a different conclusion.

So that's the challenge for all of us because it's stretching, you know, for us to think about data and talk about data in a different way, but I think we have an opportunity because we've got folks coming through who aren't constrained by the one or two dimensions that we've traditionally looked at, but we do have to provide really positive reinforcement for

that kind of culture and bracing the diversity of views and not letting it frustrate us in terms of, you know, what some may want to do as a quick win.

DR. CALIFF: I really appreciate that comment, and I'll just say, you know, I'm old enough now to say this. In every industry and academic setting, you can readily see the differences between environments where this sort of collaboration you described is promoted and rewarded and where it's not.

You know, many of you are probably not basketball fans, much less Duke basketball fans, but I learned a great lesson, Coach Kay, the famous coach, you know, teamwork is his entire theme, but one year, he hurt his back and he was out for most of the season and the team completely fell apart. He still had, you know, centers coaches, forward coaches, guards coaches, but he realized and he lectures about this, he realized then it wasn't enough for the leader to reinforce it, he had to instill that way of thinking in the next level down and leadership and management and I completely agree with you.

Of course, it's easier to say this than to do

it when you're under pressure to get a decision made within FDA, etcetera. So thanks.

DR. KOWALCYK: Okay. Dr. Woodcock, you have your hand raised.

DR. WOODCOCK: Yes, I just wanted to comment that the Center for Drugs, before the pandemic, you know, had worked on reorganizing the process for its review of the new drug applications and the INDs, and it was specifically about team science and how to have a process that enables that robust exchange of views, not at the end but during the process.

They had, you know, lecture series on team process and team science and a variety of changes that would enable this and some studies that were done showed that the interactions significantly increased and particularly we're looking for earlier in the process that there would be interactions, not at the 11th hour.

Now that has not always occurred because it's very difficult to change culture, but I think that's probably a path forward. Thanks.

DR. KOWALCYK: Dr. Ryu.

DR. RYU: Hi. I am Dojin Ryu. Again, thank you very much for the high-level overview of the initiatives and laying out these discussion questions.

I'll try to piggyback on the comments made and try to put my thoughts regarding first two bullet points on this discussion.

Regarding data science, I think I've seen a lot of interactions, but many times it is either front-end or the back-end meaning either validation or the formulation of the hypothesis or the interpretation of the results, not necessarily throughout or interchange of the thoughts and ideas as team members.

` So I would say, you know, FDA as a premier science-based regulatory agency, we could, you know, bring the idea of this convergence, like going back to your previous slide was, you know, what convergence is, so that we could sort of promote or, you know, enhance the way to drive the science forward would be the one way to, you know, contribute to the scientific community as well as the regulatory science.

DR CALIFF: Thanks.

DR. KOWALCYK: Okay. I personally had just a

comment that I wanted to piggyback on that and then we're going to move on.

But I think one of the big challenges is when you come back to culture, personally as a statistician, I can't tell you how many times I am brought in at the end of the day after all the data's been collected and asked to fix a whole mess of problems or I'm brought in at the beginning and then I never hear anything again till the end of the day.

But also I just wanted to comment because most of the comments we've had during this discussion have been around kind of clinical and medical arena, and I began my career in the pharmaceutical industry and then I moved over into food safety after about 10 years, and I can tell you that the use of data analytics in the food safety arena is light years behind where it is in the other areas that FDA regulates and there really needs to be a concerted effort in my opinion to improve the use of data in food safety and other food-related fields.

So I personally stand -- I'm not speaking on behalf of the committee. I personally stand ready to

work with you, but I'm happy to hear the extent of interest through the comments from the board members on this topic.

DR. REISS: I think it's just a critical need not only for the FDA but for -- this is Ted Reiss -- critical need for the FDA as well as sort of the world in general and I think any -- I certainly would be interested in helping and, you know, I think we should take this on as a board to help the Commissioner in his thinking here.

DR. KOWALCYK: Thank you very much.

So we're a bit behind schedule just by a few minutes, but I don't know about anyone else, but I need a five-minute break to stretch my legs and so while we're queuing up our speakers from the Public Hearing portion of this meeting, we're going to take a five-minute break and we're going to reconvene promptly at 11:18 and so just a few minutes to stretch your legs, take a bio break if you need it, and we'll see you back here at 11:18.

Rakesh, anything to add?

MR. RAGHUWANSHI: No. We'll work to get the

public hearing presenters temporarily promoted to panelists during this break. So those who have a speaking slot please stay at your computers. You'll see a popup that will invite you to be promoted to panelist and then there is a schedule that we're going to follow so you'll speak when you're recognized by the Chair. Thanks.

DR. KOWALCYK: Okay. Thank you. We'll see you in a few minutes.

(Recess.)

DR. KOWALCYK: Okay. It's time for us to reconvene.

Rakesh, is that good on your end?

MR. RAGHUWANSHI: Absolutely, Barbara. It is a go.

DR. KOWALCYK: Okay. Great. We will now conduct the Open Public Hearing portion of today's meeting. Both the Food and Drug Administration and the public believe in a transparent process for information- gathering and decision-making.

To ensure such transparency at the Open Public Hearing Session of the FDA Science Board

Meeting, FDA believes it's important to understand the context of an individual's presentation. For this reason, FDA encourages speakers at the beginning of their oral statements to advise the committee of any financial relationship they may have with a company or group that may be affected by the topics of today's meeting.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I would like to acknowledge that the Science Board received written comments from several stakeholders and want to assure you that we have read those submissions and take them under advisement.

I understand there are seven requests to speak today. So we will proceed down our list. For our public speakers, who I believe are all now on the line, you have temporary panelist access and you are able to unmute yourself when you speak.

We understand that there are some technical difficulties. So if we are unable to get your speaker to work, please stand by as we move on to the next

speaker and come back around to you as we work to resolve any issues.

Please monitor your e-mail for one of our FDA team members to reach out to you if there are any issues during this Open Public Hearing.

Let's begin. So our first two speakers are Joseph Dever and Sibyl Swift. You now have the floor.

Open Public Hearing

MR. DEVER: Thank you very much, Barbara. It’s a pleasure to be here today and I just wanted to briefly introduce myself.

I'm Joe Dever. I'm the Director of Toxicology at NSF, and we're a not-for-profit public health and safety organization with a mission to improve human health. The group I lead within that organization is the Toxicology Team and our core expertise is in the area of ingredient and chemical safety risk assessments and we do serve a variety of both internal and external stakeholders in this area.

So with regards to CBD, our team has spent many hundreds of hours of time reviewing, assessing, discussing the available safety data and developing

what we believe is a strong science-based perspective on the topic.

My intent today is really just to share a few high-level observations that we hope can be of benefit on this topic from a public health perspective.

So the first observation I'd like to highlight to the Board really is the pace at which the body of CBD safety data is expanding. Really, it's a situation of length and you might miss another study that's been published or entered the public domain in terms of CBD safety.

In our team, we reviewed at least 16 repeated dose animal studies that have evaluated CBD toxicity, 10 animal studies around CBD toxicokinetics, eight in vitro genotoxicity studies, and over 50 clinical trials, in addition to the epidialect studies that have also been put out there.

This isn't even to mention the numerous studies exploring all the mechanisms of action regarding CBD and potentially efficacy, as well, for cannabinoid and separate binding, and I think it bears mentioning here that some of the highest-quality

studies we've seen have become available just recently over the last year or two and so a risk assessment standpoint results from what you might call the traditional battery of toxicity studies, particularly those most relevant to food and dietary supplement applications, like the 90-day sub-chronic toxicity study, are already in the public domain.

And so my first point to make here really is just that it would be our hope that these studies or at least the subset of those need to be from the highest quality could be leveraged for their full value in the public discourse around CBD safety and I've heard a lot of great discussion today around data science and how to integrate that in the framework and I think there's good opportunity here to do that with CBD.

Second observation I'd like to make is simply around some observations we've seen in this data that I think are really important and one of those is simply that the ABME, the profile of CBD in humans, it appears to be markedly different than in animal toxicity models.

So it appears that both rats and mice

metabolize CBD quite differently than humans, humans producing much more of a 7-carboxy metabolite versus some of the other animal models, like mice, producing more of a different metabolite.

So the role of these really in terms of the overall toxicology profile is not entirely clear yet. I think this is an opportunity for some target studies that can come out to help verify that situation.

This leads to kind of my final observation today which is that really based on some of these differences that we see, they're quite substantial. It's really our viewpoint that this is a great opportunity to leverage nouns.

Utilizing human cell lines, multi-compartmental approaches, in concert with human clinical data, as well, to fill these data gaps in a targeted, pragmatic, and mechanistic way.

We believe that the purpose methods already exist that could do this, but they do require flexible approach to be effective, but we do think that this work could be done relatively quickly when leveraging in concert with the data that's already out there.

So with my remaining minute here, I'll conclude by just suggesting to the Board with regards to CBD that based on our fairly extensive examination of the available data we think there's been a lot of progress in the understanding and safety profiles of CBD. We think there are high-quality studies out there that could be acknowledged and incorporated in the public discourse really with the goal of aborting more redundancy, especially in the realm of animal toxicity studies which have been useful in gaining insights, but we feel that our assessment of the data to date, the gaps that remain can benefit from a real modern approach, holistic weight of evidence approach using fit for purpose modern tools, in vitro, and silicon tools, and we think there's a really great opportunity to apply those tools which have really, I think, come to light for the past five years for public benefit.

So I appreciate having the opportunity today to make these remarks and be here today and I am happy to address any follow-up questions if there are any now or later, and that concludes my comments.

Thank you very much.

DR. KOWALCYK: Thank you. Does the Science Board have any follow-up questions for this presenter?

(No response.)

DR. KOWALCYK: Okay. I do not see any hands raised. Thank you very much.

Our next presenter is Sibyl Swift.

MS. SWIFT: Thank you, and I am the Vice President for Scientific and Regulatory Affairs at CBMD. So I am an employee of the company just to be in full disclosure.

So I'd like to start by saying thank you to the agency the Board for giving us a opportunity to provide comments today.

I'd like to reiterate what my colleague from NSF stated. There is a large amount of information related to CBD data and safety data on the market right now, not only publicly-available literature but also being generated by companies worldwide.

For example, CBDMD submitted a novel food dossier to the EU in the U.K. We were validated by both regulatory agencies as one of the first nationally-derived cannabinoid dossiers. Furthermore,

we anticipate approval in the U.K. in the next few months.

The agency has posted guidance documents and held numerous scientific meetings, opened the docket for submission of cannabinoid safety data, and in the face of all this data and testimony from medical professionals, we just keep hearing the question asking for more.

The safety study that CBDMD executed on our broad spectrum extract covered multiple systems and was more than sufficient for the rigorous review in the U.K. and the EU. The FDA is refusing to review our data.

The dietary ingredient notification has generally recognized that notification processes are well established and accepted for review of new dietary ingredients. These processes provide the agency with the ability to thoroughly review safety data and to request additional data if there are gaps.

As a specific example, CBDMD conducted an extensive literature review and gap analysis prior to conducting the safety studies I've mentioned covering

multiple physiological systems. This data showed that a serving size that would be considered a supplement extracted from a botanical ingredient. Instructions for use provide adequate information on how to consume the product and warnings for sensitive populations as guided by the safety studies.

The manufacturing process is repeatable and consistent and it's been certified to a dietary supplement CPMG standard by NSF.

The work conducted is more than required for self-grasp notification and/or other such notifications. This data has been reviewed by multiple toxicologists and is currently under review by both U.K. and the EU. It's beyond challenge. It's been offered to the agency to demonstrate the safety of our particular ingredient.

Despite all this, we keep being met with refusals to accept the submission and review of the data. So we have filed a citizens' petition with our trade association, the Natural Products Association, requesting that the extensive set of data compiled in our safety studies be provided the same opportunity for

review in the U.S.

Our study explored many of the endpoints for which FDA has expressed concerns, including repro-tox and gene-tox. Our petition also provides the basis for why we believe CBD is not drug-precluded. It is in fact a new dietary ingredient and should be given the opportunity to demonstrate its safety using the new dietary ingredient notification process.

But my remarks today are not an advertisement for our petition or our case. I'm here to speak on the process of demonstrating safety of a new botanically-derived dietary ingredient.

The notice for this meeting stated that the agency's concern challenges for the evaluating safety of supplements with predicted pharmacological activity, specifically highlighting cannabinoids for today's meeting.

I'd like to be clear. Cannabinoids are not the first constituent of a botanical dietary ingredient to exhibit pharmacological activity. There are a number of other ingredients that have a long history of use in dietary supplements while exhibiting

pharmacological activity, including caffeine, EGCG, EPA, DHA, carnitine, barstine. Commonly-consumed foods exhibit pharmacological activity. For example, there's a paper published that honey can exhibit anti-inflammatory effects through toll-like receptors.

Should we be questioning the safety of honey or an extract from honey due to its pharmacological effects? It's misplaced and, quite frankly, misleading and disingenuous to blindly state there are concerns about pharmacological activity in a dietary supplement by using the word "pharmacological" instead of biological or physiological.

It appears as though the agency's attempting to characterize this particular set of ingredients in cannabinoids as a drug. By contrast, it’s well established that dietary supplements can have biological and physiological effects on structure or function in the body.

The structure or function notification process is defined in the FDA site as follows: "Structure function claims may describe the role of the nutrient or dietary ingredient intended to affect the

normal structure or function in the human body. Notifications may characterize the means by which nutrient or dietary ingredient acts to maintain such structure or function. For example, antioxidants maintain cell integrity."

This is distinct and separate from the question of if a dietary ingredient is safe. Food is well known for having biochemical and physiological effects on cells, tissues, and organs, otherwise known as pharmacological effects. Combine that with the fact that dietary supplements, food ingredients, are not intended to be ingested in certain sizes but would be considered pharmacological or for indications that would be actual drugs.

They absolutely will have biochemical and physiological effects. So I think we should look to history for clarity. If the dose makes it poison, we shouldn't be asking whether an ingredient has pharmacological activity, we should be asking is it safe?

The standard that FDA is attempting to establish for dietary ingredients using cannabinoids as

the poster child stifles innovation. Are we prepared as an industry to accept that arbitrarily high standard as the new norm?

So thank you for allowing me to speak today. Are there any questions about my comments?

DR. KOWALCYK: Thank you. Do any members of the Science Board have any comments or questions for the presenter?

DR. BAHINSKI: Hi, this is Tony. Just one quick question. Tony Bahinski.

It looks like the EU has actually put a halt pending review of safety for CBD. So I think that's in contrast to what the speaker's comments were that they were moving forward.

MS. SWIFT: Actually, we participated in the estimating parts of this meeting this morning at 9:30. Our dossier met with all of the objections and questions that that particular agency has raised and so one of our consultants in the EU has spoken with the representatives and asked them to look at our notification specifically because the gaps they have suggested exist were met with our dossier and with

those safety studies. But thank you for that question. That's an excellent point.

DR. KOWALCYK: Thank you. Any other comments or questions from the Science Board members? Again, just a reminder to please raise your hand if you have some.

Okay. I do not see any hands raised. So we will move on to the next speaker. Thank you very much.

Our next speaker is Vicki Seyfert-Margolis and Reggie Gaudino. My apologies if I mispronounced your name.

DR. SEYERT-MARGOLIS: Can you hear me?

DR. KOWALCYK: Yes, thank you.

DR. SERYFERT-MARGOLIS: Great. Hi, I'm Vicki Seyfert Margolis, and I'm currently the CEO and Founder of a company, My Own Med, which is a customizable digital platform that supports decentralized clinical trials and health workflows.

Today, I also know some of you because I actually worked at the FDA for several years as the Senior Advisor for Regulatory Science and Policy to Commissioner Hamberg, and I know Dr. Sarwal through my

work as the Chief Scientific Officer of the Immune Tolerance Network which was a large public-private clinical trials network supported by NIAID.

I'm coming at this from a bit of a different perspective which is as part of an organization called The Council for Federal Cannabis Regulation and as a representative of their Scientific and Regulatory Affairs Committee.

In addition to me, my co-chair is Dr. Reggie Gaudino, who is a molecular geneticist focused on the biochemical networks in plant phytobiochemistry with an emphasis on CBD.

In addition to some of the people on these slides, CFCR has assembled a team of scientists, entrepreneurs, regulatory lawyers, representatives of the cannabis enterprises, pharmaceutical, neutraceutical, consumer packaged goods, wellness, etcetera, to really try to take a look at how we can bring a smart regulatory approach to this very challenging and complex product.

We believe that good policy comes from good science and the CFCR is a nonprofit organization. We

are really working hard to address the unique issues and challenges that are related to cannabis and that must be addressed to develop a science-based regulatory framework for drugs, foods, dietary supplements, veterinary products, and cosmetic products.

We believe in supporting FDA's access to and helping to support aspect to desperately-needed resources within the agency to take on this challenging regulatory framework and challenging product, hopefully bringing help in the form of independent scientific and regulatory experts and to help bring together current data and research on cannabinoids in order to help the FDA operate within and advance a 21st Century approach regulating a wide variety of beneficial products, be able to buy a plant that has been federally illegal for eight decades but by now is in widespread use through state legalization.

We have submitted written testimony and I'm giving a brief excerpt of it.

So while we recognize that the FDA has already developed a regulatory approach to cannabinoids via the Drug Pathway, including the approval of

Epidiolex, the widespread utilization of cannabis under state utilization products has created challenges and we want to be very clear in the composition section of this that we recognize that THC or the THC components will need to stay and it is our belief will be in the clinical realm of potentially in a totally different framework for adult use and in a recreational format.

We are really here more to address the cannabinoid and CBD, but we just wanted to mention that, and we also recognize that the cannabinoids come in a wide variety of forms or compositions, starting from the plant, moving forward into complex extracts, purified extracts, and into bio-synthetics.

Existing research indicates that CBD and other cannabinoids may hold great promise as therapeutics in disease treatment and prevention and it appears likely that drug development pathway will be utilized to address these pharmaceutical uses, including the use of drug claims.

However, unlike many new drugs, there is a long history of cannabinoid use prior to and after legalization in multiple use states and so we believe

this broad utilization can afford the opportunity to look at historical data as well as the need to generate new data in conventional studies, real-world approaches, so that we can obtain much-needed data about the safety and benefits associated with cannabinoids.

We also believe there needs to be significant attention placed on developing standards for purity, dosing of CBD, and other cannabinoid products in order to better evaluate the risks and benefits of cannabinoids for consumers.

So the goal of CFCR this morning and this afternoon is to raise and discuss with the Science Board and the FDA the creation of a foundational set of data hopefully using a collaborative approach and a protocolized approach with industry players that will allow for us to address some of these very important issues, including dose-related safety events in humans, for the benefit of streamlining regulatory approvals and to set a foundational knowledge of science.

We propose further evaluation of animal and human toxicology data to date and identification and we

hope to help with the identification data gaps with the development of master protocols or strategies that can be used to address dose response safety events in healthy humans and ultimately to use data that will be developed or derived from clinical trials treating humans with different diseases.

We recognize that there's been data published in the Epidiolex filing and additional data that's been published in journals, such as *JAMA*, demonstrating that there may be benefits of cannabinoids, for example, in emotional stress and exhaustion in front-line health care workers, but also notably there were some adverse events with respect to increases in liver enzymes which were noted in these published studies.

We hope to use this sort of a framework to help identify critical elements. Of course, the range of products that exist and to that end, CFCR has begun to outline this and, for example, to try to create tools, educational information, and to gather and convene experts so that we can help understand what is the complex nature of this product. How can we develop and derive data that will support understanding, what

are the safety dose considerations in all of these different complex product compositions, how we can drive standardization of products, and, of course, how we can use and build on base of knowledge to identify areas where more data is needed to help the FDA to find the best strategies for obtaining such data most efficiently and cost effectively.

Thank you for the opportunity to speak to the Science Board today.

DR. KOWALCYK: Thank you very much. Are there any questions from the FDA Science Board for this speaker? Again, just a reminder, please raise your hand and I will call on you.

Okay. I do not see any hands raised. So we'll move on to the next.

The next speaker is Gregory Gerdeman.

MR. GERDEMAN: Hello. Let me see if I can share this. Can this be seen? It's very brief, just some bullets.

My name is Greg Gerdeman. I don't have time for long credentials, but thank you for allowing me to have comments. I have 25 years of experience with

cannabinoid pharmacology, dating back to my time as a graduate student at Vanderbilt University in the '90s where I did endo-cannabinoid research, and it spanned academic and industry.

I have advised a number of cannabis and hemp companies over the years. Presently, I have a scientific advisor role with a company called Tennessee Pharmaceuticals but no other real interest in the industry, other than my academic interest, and I suppose I'm offering myself at your disposal for some of these broad level pictures that I think are important for anyone advising the FDA.

First of all, on this point, I feel like it's appropriate in this kind of forum and on this subject to insist, at least for the public record, that prior to FDA approval of Epidiolex, CPD was certainly consumed by the public in certain areas.

For what it's worth, contention that Epidiolex was, quote unquote, first is indefensible honestly. I saw in early 2000s I West Coast sort of medical marijuana collectives, a lot of breeding for high CBD varietals and artisanal extracts that had CBD

in them and were used in the community. I saw chromatographic proof of CBD, although it wasn't published in a way that could represent prior art, so to speak, and this, of course, influences the recognition per the Food, Drug, and Cosmetic Act of CBD now being seen as a drug and an adulterant rather than something that has dietary use. It was present in, of course, Europe dating back centuries.

Of more direct importance, I think I want to say a few things about the safety profile of CBD and including what was just briefly momentarily mentioned a moment ago about liver toxicity seen in the Epidiolex clinical trials.

Again, I think it's really important to know the polypharmacy context of that clinical experiment. First, prior to that GW conducted studies with CBD as an ingredient both in apixomals and as a solitary extract in the early 2000s in elevated liver enzymes and signs of hepatoxicity were simply not seen. This comes to me for years from a long-time friend and colleague, Dr. Ethan Russo who was the pharmcoviligance officer on those studies.

And then subsequently, years later, Epidiolex was in trials for Gervasin and there was evidence of elevated liver enzymes, but by mandate of that study design patients were not taken off their existing therapies despite the fact they weren't working and it very notably included the anti-seizure medication Valproic acid which is very well known to be hepatoxic and neurologists considered it a terrible molecule to use with other substances that could impair its hepatic metabolism.

So CBD and Epidiolex was never really tested as a monotherapy but was tested in conjunction with known hepatoxic compounds. A long history of frequent animal research, although it was duly noted that animals metabolize cannabinoids quite differently in some regards, has supported CBD safety and some very recent observational studies put out by a company called Valid Care with which I have no connection has found that consumers using a variety of over-the-counter commercial CBD oils daily for over two years did not show elevated liver enzymes of any concern, and I can help you see that data if you have not seen it

yet. Again, I'm not associated with that company.

So sort of the overall point of my experience of over 20 years in developing this field, CBD extracts and islets can be manufactured very safely under CGMP and other standards. That should be a minimal concern for public safety in the diet as far as I steadfastly believe, but in the absence of more regulation, a lot of products are not produced that way and there are a lot of products with shoddy quality control, mislabeled ingredients, and so forth.

In my minute left, I want to try to just push out two other comments that I think are important for anyone advising the FDA to be cognizant of.

One regards the great need for greater pharmacovigilance and regulation over something that is not regulated at all which are the CBD-derived synthetic isomers, the synthetic cannabinoids, very popularly including Delta-8 THC, and just the slightest of comments, there are many unknown contaminant reaction products that come from the synthetic industry that create Delta-8 THC. This has been well reported by Dr. Crusidala, for example, from Purvadi Labs and

others.

I've got great concern with more potent designers sort of cannabinoids, like THCP and THCO acetate, and lastly, I want to say that the FDA should not be concerned over cannabinoids and the use of hemp grain as an animal feed. The FDA is very comfortable with regulating oil seed production and the products that go into hemp grain production are not containing cannabinoids.

Ranchers will not scale up for efficiency in ways that include cannabinoids and I hope in a time of food scarcity that regulating this nutritious grain source can be done in a way similar to other oil seeds without misplacing too much emphasis on cannabinoids.

Thanks for giving me this chance for a somewhat distinct set of comments and I consider myself at your disposal for conversation or discussion and I welcome any questions. Thank you.

DR. KOWALCYK: Thank you. Are there any questions from the Science Board for this speaker? Please raise your hand.

Okay. Seeing none, we'll move on to the next

speaker, Elizabeth Baker.

MS. BAKER: Hello. First, I would like to give thanks to the FDA and to the Science Board for the information that was provided this morning on FDA's new alternative methods activities. I'll refer to the new alternative methods as NAMS in my brief comments.

I'm Elizabeth Baker. I am the Regulatory Policy Director at the Physicians Committee for Responsible Medicine. We're a nonprofit supported by about a 175,000 members who are working for effective, efficient, and ethical research and testing.

Last month there was an article published in *Forbes* that did a really nice job of highlighting the urgency of implementing human-specific approaches for evaluating drugs and other products.

According to the author, 208 patient deaths and 10 liver transplants resulting from the toxic drugs in the study could likely have been avoided had the human-based liver chip been used.

This article is a really nice reminder that there are great reasons to do this work of implementing new approaches that center on health and scientific

innovation, in addition to sparing animals from being used in tests that will often result in pain and death.

Today, there's been a lot of talk about maintaining current safety standards, but I want to make the point of this is really about improving the standards and these methods offer the possibility to do so.

So in agreement with the author of the *Forbes* article, our team thinks it's really important that FDA be willing to take a hard look at these studies, at the models that we're using, and being willing to embrace new approaches that better reflect human health.

In recent years, it's been really nice to see the agency shifting its thinking with regard to NAMS. This has been evident in reports from the Commissioner, like the one that Dr. Strauss shared today, that affirms FDA's goals of integrating new science and reducing animal use, the launch of FDA's Predictive Test Roadmap, the Alternative Methods Group, the Ice Dam Qualification Program, and the Animal Welfare Council, and more.

And so from our perspective, these activities

really have set a nice foundation, but we need to see more funding. They need to be developed further. We'd like some more transparency. We also think that policy change must be implemented to really complement these efforts.

We've been on the Hill advocating for funding to support FDA in this qualification and NAM integration activities. So it was really great to see the Fiscal Year 2023 President Budget Request included five million for new alternative methods and the program that Dr. Strauss covered today.

I believe that FDA's qualification programs have the ability to really revolutionize product development by providing a process for methods to be qualified.

I also think we need a lot of improvement around efficiency and timelines compared to the current programs. Patients are suffering and dying of toxicities while we wait to qualify these new methods that may be able to better detect these toxicities than the animal studies.

So we hope that Congress will appropriate the

funding and we'd like to see some transparency around the program's activities and output as well as the opportunity to provide input, for example, through a public meeting or commenting period.

One thing that we hear time and again from industry is that FDA's written policies don't support the use of newer science. So many of FDA's regulations are still referencing animal data, guidance recommend animal use, some guidance has conflicting information about utilizing different animal tests, and actually some guidance includes some language that indicates intent to allow for use of NAMS, but there's no real guidance around how to make that happen.

So we request that the agency and that the Board advise the agency to update its written policies, do a review to see what needs to change so that the regulatory framework does keep pace with science. We can move the requirements for animal use, broadening it to more clinical which will then account for these newer approaches, and then doing a very thorough review of guidance to industry because, as I mentioned, there's a lot of conflicting information.

It used to be the case that the non-animal methods were evaluated against animal data, but this thinking and practice is shifting for NAMS meant to assess risk to humans. Human relevance is the important consideration and should be prioritized.

We know that it's not always available, but we think there's a lot there and the President's Budget Request included 7.5 million for NCTR to do comparative studies to evaluate NAMS. They will compare side-by-side the traditional animal tests to NAMS and it would result in the death of many new animals for NAM evaluation.

So for NAMS intended for testing human products, this is a step back with regard to science and ethics and we actually think a lot of this could be avoided by NCTR working with FDA centers and interagency partners, such as the National Toxicology Program, to utilize existing data.

As far as animal welfare and FDA science goes, in 2018 the FDA established its Animal Welfare Council. We really haven't heard any updates on this and we'd like some transparency around whether the

group still exists and what it does, and I think one potential project for the group would be to help us get an understanding of the actual numbers that are being used for FDA purposes.

So FDA has committed to this goal of reducing animal use if there's not really a process for accounting for the animals used and without an approximate accounting, it's really hard to understand how we can even measure progress toward the agency's reduction goal.

Finally, NGOs, I think, can be a great resource to FDA. The NGO staff have ideas. We have scientific and policy expertise. We also have extensive experience with training regulators and industry scientists and we've heard today multiple times about the need for collaboration. We agree, but NGOs were left off the agency's list.

So I'd ask the FDA and the Board as part of NAMS' efforts to host stakeholder meetings to explore how the NGO resources can be best utilized and also to seek some NGO input on the subcommittee efforts that will form as a result of today's meeting.

That's it for my comments. Thank you.

DR. KOWALCYK: Thank you. Are there any comments or questions from the FDA Science Board?

Okay. Seeing none, we will move on to the next speaker, Michelle Peace.

` DR. PEACE: Good afternoon. Let me pull my screen back up. Okay. You should be able to see that now, correct?

All right. So good afternoon. Thank you so much for giving me the opportunity to present our research findings from my team at VCU.

I have more than 20 years of experience as a analytical chemist and a forensic toxicologist. I've been funded by the National Institute of Justice to study vaping drugs other than nicotine. My research has characterized the rising unregulated hemp and CBD industry.

The hemp and CBD industry is largely unregulated and its quality assurance support is inconsistent throughout the CBD industry. Even though once a boom, we now have some understanding that the CBD market is projecting weaker growth.

So what is it going to do with all of this expensive surplus? It can be converted into a cannabinoid that provides psychotropic effect. With time and strong acids, CBD can be converted to Delta-8 THC. The conversion will produce both Delta-8 and Delta-9 THC. The chemical that's used in synthesis could end up in the final product that a consumer buys.

The unregulated industry is calling Delta-8 products hemp-derived because Delta-8 is a natural cannabinoid and is converted from natural CBD. Make no mistake, the Delta-8 THC end products is synthesized.

This honey stick was supposed to have only 45 milligrams of Delta-8 THC. It precipitated some of the most terrifyingly strong hallucinations an experienced cannabis consumer ever had.

We found more than 900 milligrams of CBD, 200 milligrams of Delta-9 THC, and more than 630 milligrams of Delta-8 THC in this honey stick purchased at the same time as the one consumed.

If we assume that the natural plant contains one percent of Delta-8 THC which is generous, 14 pounds of plant material are needed to make this single honey

stick. This is economically not feasible. Therefore, we can say that Delta-8 found in this sample was synthesized.

Anecdotally, the effects of Delta-8 are mixed, but we do not know how much drug is in the products people consume. In the Martin tetrad developed at VCU that assesses activity at the CB1 receptor, three of the four assays showed that Delta-8 and Delta-9 are equally potent and efficacious.

When we received this hemp drive product, I thought it contained zero THC, misunderstanding what THC zero meant. This came in as a case in which somebody had violent hallucinations that precipitated a significant crime. We identified THCO or THC acetate. Supposedly it is more spiritual or two two one-hundred times more potent than Delta-9 THC.

We believe this is only the tip of the iceberg. These analogs are reasonably easy to synthesize for enterprising persons. It is possible that from these structures alone hundreds of other analogs can be formed.

A two-year-old accidentally ingested cannabis

candies at a swim meet in rural Virginia. It was labeled as Delta-8 and had a significant adverse reaction. However, we analyzed the product and found that it only contained Delta-9.

We have also tested more than 60 products purchased in surveillance testing in the Commonwealth of Virginia. These two products contain residual solvents presumably used during manufacturing. This product consistently contains at least twice the Delta-8 THC concentration, no matter where it's purchased and no matter how many times we purchased it.

This smokable hemp cigarette is actually not plant material. It is shredded paper that has been sprayed with Delta-8 and rolled into cigarette form, and this cookie product was still wet, smelled of solvent, and contained hair.

We are still not sure what is growing on top of this date product. This product appears to contain medical grade gummy candies, but it is really plant product inside the package. This apple cider sold at a fair didn't contain any CBD at all, and these moon rocks failed the microbial testing.

The most compelling data we have regarding the consumer safety and public health gaps are the testimonies of persons who purchased CBD products for therapeutic benefit and had adverse effects.

We conduct untargeted chemical analyses to discover all chemicals in a product. The experiences of persons from the top five products are not surprising because of the presence of synthetic cannabinoids. The last three cases were women who reported having strong adverse reactions. Their products contained only natural cannabinoids.

It is not known what other medications they were taking. We do not know what precipitated the adverse events, other than they had these effects immediately following consuming the products. The women had no idea who to reach out to.

So there's so many points that can be made in summary, but advancing research and public education are key. Consumers believe mythology, preliminary data and poor science regarding the effects of cannabinoids. When robust studies emerge years later, consumers showed mistrust and disdain oftentimes for real

science.

Educational campaigns and informational portals must be funded to inform the public about products sold online and in stores. The pervasion of these products in our communities warrants a strong unified effort. Misinformation and mythology reign in small communities.

So on that note, on that really awful last note, I do want to thank the FDA for holding this meeting and I am certainly at your disposal if you are interested in any other information that is coming out of my research laboratory. Thank you.

DR. KOWALCYK: Thank you very much. Do any of the Science Board members have a question? Dr. Afshari.

DR. AFSHARI: This is Afshari. Thank you. I had a question related to your comment around the potency of the various THC forms, and I was just wondering in your opinion, are there reliable and standard biochemical assays or methods to determine that potency across the various forms?

DR. PEACE: I do. The assay that I

referenced in my talk is the Martin tetrad that was developed here at VCU. This assay has been used for decades. It was originally developed to study the synthetic cannabinoids that were being generated, the Data BUH compounds particularly and certainly the compounds coming from Pfizer.

So this assay has been used by VCU's Department of Pharmacology and Toxicology for decades to assess activity at the CB1 receptor.

DR. AFSHARI: Thank you.

DR. KOWALCYK: Thank you. Are there any other comments or questions? Dr. Ryu.

DR. RYU: Hi. Is there any surveillance data from other states in terms of the prevalence of the synthetic cannabinoids?

DR. PEACE: I think that is a great question. So there are only a handful of small studies that tried to capture how pervasive these are. There was a study that was just released, I believe it was conducted by a cannabis quality assurance lab, I believe called Prevarity, and we also do quite a bit of surveillance studies ourselves.

The real challenge around this is that particularly for untargeted analyses and because of the depth of the analyses that have to be conducted, it's expensive and funding support for these kinds of analyses is oftentimes very difficult to get.

So I would say a lot of the data is coming out of our crime labs and forensic toxicology and controlled substances sections of those labs, as well.

DR. RYU: Thank you.

DR. KOWALCYK: Thank you. Are there any other questions or comments?

Thank you very much. We will move on to our last presenter, Elias Jackson, and I believe he will be presenting with Charlotte Thompson and Alan Shirley, if I got that correct.

DR. JACKSON: Yes, hello. This is Dr. Elias Jackson from Vyripharm Enterprises, and I want to thank the Scientific Board and the FDA as well as the previous speakers.

We would like to present to you today a solution to some of the challenges that have been brought up over these talks for today.

Vyripharmaeuticals and Vyripharm Enterprises is a biopharmaceutical firm located in the Texas Medical Center Innovation Institute. Our focus is the integration of traditional pharmaceuticals with novel and alternative pharmaceuticals.

So what we want to talk to you today about is beyond sale integration. We believe that this will answer many of the challenges currently facing this industry.

Now Vyripharm Enterprises owns over 50 patents and we are focused on building a regulatory framework which would allow the FDA to have full regulatory oversight not just from seed to sale but seed to patient outcomes.

You know, a lot of the states and I commend on their courage, but they currently are using software programs but as we well know, software programs aren't full comprehensive regulatory framework for uniform standards within the industry, and since we're talking about active pharmaceutical ingredients, it's going to be critical that these medical cannabis programs begin to collect true and solid medical data. That's the

only way the physicians in those states are going to be able to make sound decisions, sound suggestions to the legislature of those states.

But to this talk, we want to ensure that the FDA has that ability to make those same recommendations to Congress.

Now one of the most important pieces about this methodology has been recognized by the United States Government. There are three patents surrounding the methods and evaluation of cannabinoids and cannabinoid-based products for public health and public safety.

What this means is that currently the FDA could begin to implement a solid regulatory framework that would capture data from every point of the supply chain. What does that do? That brings in the DEA. That brings in HHS. All those data points that allow the FDA to begin to give Congress those suggestions, those recommendations to allow the FDA scientists, working groups to begin to tease out how do we go forward with this industry. It's right here ready to go with these intellectual properties made by Vyripharm

Enterprises.

I now want to turn it over to Alan Shirley, the President of VPH.

DR. SHIRLEY: Thank you, Elias.

I want to highlight the combined solution, you know, within a robust testing program and really it's all the testing of the critical production and supply chain. It gives you false supply chain feasibility, for instance, a recall process.

The emphasis on regulatory compliance but also a holistic approach to quality via the growers and how they manage their production.

You know, the actual test platform is based on a transaction and then tracking it, you know, to measure safety and quality and we're leveraging data as early as possible in the supply chain to react to that and also to do what we call process within that supply chain.

Here's an example of an adoption of new rapid testing technology to assist law enforcement. This particular technology is handheld THC monitors where the field results are linked to the actual reporting

platform and the supply chain management for actual recall process.

I'd like to hand it over to Charlotte Parker-Thompson, the Chief Compliance Officer.

DR. PARKER-THOMPSON: Thank you, VPH President Alan Shirley.

I'd like to stress to the FDA and all other participants and the Science Board that the Medical Cannabis Certification Program for Public Safety and Public Health of VPH enables standardization, transparency, accountability, as well as supporting the regulatory and law enforcement guidelines.

Throughout the systems development life cycle, we are aligned with the product life cycle from seed to human consumption. There is microbial testing, analytical testing, quality control, and quality assurance throughout the entire supply chain.

Our training actions for this platform are available at the administrative level with respect to the grower, the tester, the data analyst, and the dispensation analyst.

Throughout the blockchain methodology, the

application allows for the certification and an actual certificate throughout the entire process life cycle. There's traceability and digital transfer of title throughout the certification process. There are over a thousand data points and data elements that are available within the application that will support the appropriate resource as well as timing throughout the process and the product processing.

We would like to encourage the ability to collaborate and work with you further with respect to the methodology and we thank you very much for the opportunity and your time.

DR. KOWALCYK: Thank you. Are there any questions or comments from the FDA Science Board members?

Okay. Hearing none, we will move along. I want to thank each member of the public who took time to address the Board today.

We will now take a 30-minute recess and return sharply at 12:42.

Thank you again to the presenters and we look forward to seeing everyone back again at 12:42

promptly. Thank you.

(Whereupon, at 12:12 p.m., the meeting was recessed for lunch.)

AFTERNOON SESSION

DR. KOWALCYK: Welcome back, everyone.

We have another very interesting meeting topic on Challenges in Evaluating the Safety of Dietary Supplements and Food Ingredients with Predictive Pharmacological Activity.

I appreciate all of the speakers making time to address us today. For this session, since we have several speakers from FDA, I will ask that each introduce themselves right before they make their presentation.

Once we have heard from the speakers, we will move on to the questions that we have been asked to consider for this session.

For the Science Board members, if you should need a point of clarification or have a question during a presentation, please use the Raise Your Hand function to get my attention and I'll attempt to find a time to interject to ensure you can ask your question.

Apart from that, once we get to the Q&A and discussion portion after the presentations, please utilize the same procedure to get my attention.

I understand we will begin with Dr. Woodcock. Again, welcome, Dr. Woodcock.

CFSAN Session: Challenges in Evaluating the Safety of Dietary Supplement and Food Ingredients with Predicted Pharmacological Activity

DR. WOODCOCK: Thank you and could I have the slides up? Thanks.

All right. Well, as the Chair has already stated, we're going to present about regulatory oversight for various substances. You've heard from some of the public speakers already about their interest in these cannabinoids and from various points of view.

The purpose that we're consulting you for today is, Number 1, to fill you in on all the research we've done, all the information that we have collated since we began looking at this issue, and we'll talk about the history in a minute, but we have gathered a great deal of information but we still have numerous

scientific information gaps and so we're very interested in your input on how we can fill in these scientific gaps.

And then we are going to be asking you about the overall safety assessment and risk management that's related to these type of substances.

What we're not going to be asking you about is any specific regulatory pathway and how appropriate it might be.

We know you're not regulatory experts. We are giving you some tutorial, all right, on the different regulatory pathways during this session so that you understand the scope of types of regulatory frameworks that we have, particularly in foods but also across other parts, and as you've heard, these compounds are being used in many different manners of administration, shall we say, different substances, but we're not really here to discuss whether we should use one or another different regulatory pathways. We would not put that burden on you. We're asking for science.

So next slide. So you see a cannabis plant has bioactive compounds, known as cannabinoids. We

heard a little bit about the analysis, the chemical analysis of some of those recently, and the plant itself, THC and CBD are the most prevalent cannabinoids, but as one of the public speakers said, of course, the strains can be manipulated and grown in order to stress one type of cannabinoid over another.

But these two molecules, cannabinoile and Delta-9, are very similar in structure, as we already heard. THC, Delta-9, is the compound responsible for the high in cannabis, but CBD is also bioactive.

Next slide. So the history of this, this dates from 2018 in the Farm Bill, which removed hemp from regulation under the Controlled Substance Act, and, of course, this was intended to open up agriculture to growing hemp for a wide variety of things, like clothing and rope and so forth.

But it was removed from Schedule 1 of the Controlled Substance Act and defined hemp as the plant cannabis sativa with Delta-9 THC not more than 0.3 percent on a dry weight basis, and this includes hemp derivatives, such as CBD, can be in there and can have a high concentration of CBD.

Hemp products would be subject to regulation under the Federal Food, Drug, and Cosmetic Act when that would be applicable. So if they were a drug, for example, we have a drug, Epidiolex, that is CBD, or potentially if they were able to be dietary supplements or cosmetics or veterinary products and so forth.

Okay. But hemp products under the Food, Drug, and Cosmetic Act have to meet the same standards as any other product regulated under the FD&C Act for that particular commodity.

Next slide. So CBD right now is about a $4 billion market, predicted to grow. We heard from one of the public presenters that maybe the market is flattening out, but we also heard that other related compounds may be growing in interest and marketing. Some people feel that CBD will continue to grow. That's just something we'll have to look at.

So how is CBD that became, you know, available out of the Controlled Substances Act, how is it currently sold? I'm sure all of you have seen it in stores in different formats. It's sold as tinctures, capsules, topicals, in beauty products, like cosmetics,

in vape oil and cartridges to vape, to smoke, for pets, in gummies, that's very common and has been the source of a number of poisoning problems with children, in beverages, in other foods and edibles, and as an approved drug, as I already said.

And so all these formats are avenues for consumers to get CBD, whether through, you know, inhalation, absorption through the skin, oral, and a portion of the market is the Epidiolex, the approved drug, but that's not a huge proportion of the market.

Some CBD products clearly meet the definition of products that are regulated by the FDA, for example, if they are using drug claims and so forth, but others may not be at all clear.

Next slide. So why do people use CBD products? For us, when we looked at adverse events, so this is people who have had adverse events and reported them to the FDA, okay, so this wasn't a broad sample, the top three self-reported conditions for suing CBD products were pain, anxiety, and insomnia. So people are taking those, self-medicating with those for those conditions.

Here you see some of the other types of uses that we've seen.

So this is purely limited as far as numbers. It's N of 16, but you just see there's a wide variety of types of conditions that people are consuming CBD for, and the premise that, you know, we feel that there is some type of biological, pharmacological activity of CBD and that people, you know, are taking CBD for a hope of some relief of some condition.

When we say this product may well be psycho-active, obviously it's neurologically active. This is approved as an anti-seizure drug and it doesn't seem to be creating a high. It does seem to have a neurologic effect, however.

Next slide. Now this is sort of the plot thickens here, right. So interest both in the people who sell these products and in the people who buy them and other cannabinoids is growing.

More than a hundred different cannabinoids have been identified to this point and we don't really understand the biological properties or pharmacologic properties of many of them.

This figure is from a study that FDA did on CBD products contained in the marketplace. Of course, that's just a snapshot, but these are some of the common compounds or molecules that are found. We also heard from a public speaker about this, although that sample was from people who had experienced serious adverse events.

But the point is compared to, say, THC and CBD, we don't know very much about the safety profile of each one of these individual molecules, although they may have been consumed by people from hemp. Their prevalence, you know, how much exposure people actually got of those is unknown, but based on their chemical structure, they have predicted activity, bioactivity which raises safety concerns.

Next slide. So there are statutory barriers that currently prevent marketing CBD in foods and supplements, although that is currently done. CBD is, as I said, the active ingredient, FDA-approved, drug and was subject in clinical investigations before it was marketed in food or dietary supplements.

So there's a food prohibition for that and

then there's a dietary supplement exclusion for products that were marketed as drugs.

Now we do have the ability to issue a regulation that would allow the use of a pharmacologically-active ingredient, you know, an approved drug, for example, or something that was studied as a drug in a food or dietary supplement, and Commissioner Gottlieb said in 2018 we only would consider doing so if the agency were able to determine that all other requirements in the Food, Drug, and Cosmetic Act are met, and that would be for that is required for food additives or those used for dietary ingredients and that's one of the reasons we're going to present you some of our different authorities and what they are like so that you'll understand, you know, the different standards that these different pathways have.

Commissioner Gottlieb established the CBD Working Group which is now the Cannabis Product Committee which I chair, started chairing recently, and, you know, one of the questions that they've been doing research on and struggling with is could CBD meet

the safety standards as an ingredient in food or dietary supplement.

Next one. And so what we've done since this, the Farm Bill, about hemp was passed in 2018, we've collected a lot of information. We've done a lot of research. We had a public meeting in 2019. We opened a docket. We've done analytical sampling of CBD products and you've seen some of the results of that.

Part of the problem is we're dealing with a large number of different molecules and that seems to be growing. Collecting information on the market and how people are using these products. We've led toxicologic studies of CBD and, of course, we've reviewed outside tox studies that have been conducted.

We've monitored adverse event reports and reached out to groups, like Poison Control Centers and others. You hear some of these come through forensic channels when a crime might have been committed, others come through poison control or emergency rooms, and so forth. Some are reported to the FDA.

We've looked at the scientific literature. We've worked with external research groups. We've

pulled the studies that were done as part of drug development, including post-market studies, to learn what we can from those studies since they followed a well-established pathway, and we issued a Cannabis=derived Products Data Acceleration Plan which is a way to try to get and utilize real-world evidence about the use of these products.

So we've done all this work. We want to present to you where we are with all this and so I will turn this over right now to Patrick Cournoyer and, Patrick, if you'll introduce yourself and then carry on.

Thank you.

DR. COURNOYER: So my name is Patrick Cournoyer, and I'm acting as a Science and Policy Coordinator for the Cannabis Project Committee, and my permanent job is as the Regulatory Scientist in the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition.

So I will continue with Dr. Woodcock's introductory information and go a little deeper into what we've been working on since 2018.

So as Dr. Woodcock mentioned, we held a public meeting in May of 2019 to obtain information from the public, from the scientific community related to FDA oversight of cannabis-derived compounds. We had over a hundred speakers present at that event and over 4,500 comments were submitted to the public docket.

Now we've maintained that public docket open since that time to provide an easy avenue for the public, for stakeholders to submit information to us that might inform our analysis as regulatory options for cannabis-derived products.

Along with that, we posted a list of scientific questions we had to stimulate the community to look into some of the things that we're concerned about. This was a rather long list and some of the things that we listed were risks related to liver injury, active metabolites in humans, such as 7-COOH-CBD, impact on the reproductive system, effects once CBD is co-administered with other substances, the impact on neurological development, potential sedative effects, pharmacokinetics and transdermal penetration, the need for long-term toxicity studies, repeat dose,

effects of different routes of administration, such as oral, topical, versus inhaled, and how those can differ, effects on pets and on food-producing animals, the potential for bio-accumulation of CBD, and effects on the eye. So these were all potential scientific questions that we raised to help provide the community with some input on where we were seeking information.

We have some ongoing studies. As part of an initial study, we looked at a 147 products on the market and analyzed them for the 11 cannabinoids that Dr. Woodcock showed you earlier and a 133 of those were analyzed for toxic elements content and the produces included a wide range, including beverages, edibles, gummies, pet products, tinctures, and now a more ambitious second phase underway looking at approximately 1,400 samples for cannabinoids and for toxic elements, and you can see here a publication that came out with the first phase of that work.

We've been using multiple avenues to obtain information on the market and how consumers are using it, including by accessing third party market research and looking at the scientific literature that speaks to

those things.

We're also conducting a study of our own toxicological studies and several of them are listed here on this slide, but it's not an exhaustive list. Many of these studies are being conducted along with the FDA's National Center for Toxicological Research.

One of the studies listed here is an in vitro evaluation of male reproductive toxicity, looking at testicular cells exposed to cannabinodiol and its main metabolites, 7-Carboxy-CBD, as I mentioned before, and the earliest data of this work have now been published and this publication you can see to the right.

A different study is looking at developmental neurotoxicity of CBD exposure in rats, and there's several other studies that are ongoing, as well, with question we have about CBD's effects.

We're also monitoring adverse event data. These come in through various avenues and FDA staff are looking at this information and looking to spot trends and are compiling this information for presentations like the data shown here.

We're monitoring the scientific literature.

As one of the public commenters mentioned before, there is a lot of research going on into CBD, in addition to the drug development pathway, and so this is screenshots from a literature review that has been put on FDA's website that was completed as of 2019 but, of course, a lot of information has come out since then. So we're constantly looking at the scientific literature.

More recently, we issued the Cannabis-derived Products Data Acceleration Plan and what that is is a portfolio of pilot initiatives and partnerships, looking to advance data-driven safety signal detection to enable us to be aware and identify emerging and new issues more readily and leverage doing different types of data sources. Work in those projects is ongoing.

So given the entirety of all of that work that we've done to acquire more information, there are things that we do know and we do know that CBD raises important safety concerns and so we've done our best to be clear and communicative to the public so that they can be informed about potential risks from CBD products.

Here I list the website snapshot where we summarize some of the key points that CBD can cause liver injury, interact with drugs, and cause reproductive toxicity in test animals.

We've taken targeted actions to protect public health. As Dr. Woodcock mentioned, the market is large and our resources are not unlimited, but we prioritize products with the greatest public health risks and we issue warning letters to select firms marketing CBD products that are marketed to treat disease or for other therapeutic use, products for food-producing animals more recently, also foods for humans and animals with added CBD, and we've indicated in those letters that we cannot conclude that CBD is generally recognized as safe for use in food.

We've also targeted CBD products with concerning routes of administration, like nasal and thalamic, and we quite recently issued some warning letters to products containing Delta-8 THC due to the risks that those pose to the public.

Now what brings us here today is that CBD and cannabinoids raise scientific and regulatory

challenges. So we know that if used outside of the approved drug context for several reasons raises important safety concerns, particularly with long-term lifetime use, but besides CBD, we know that other cannabinoids are poorly understood and so they have suspected pharmacological activity but really that raises more questions than answers and we have a very limited understanding of their respective toxicity profiles.

And so our questions to the Science Board today relate to the challenges of ensuring the safety of the substances that are like this outside of context of an approved drug.

The subsequent presentations will be looking at the different pathways for drugs, dietary supplements, and food ingredients. So just as a primer for that, I'll run through some of the key elements of each and put them here for comparing and contrasting.

Starting with drugs, the typical users are those with a medical condition. So those users are a quite defined subset of the population. The safety standards for a new drug approval is that the benefit

outweighs the risk.

So you can see that there is some ability for risks to be entering the equation but what really matters is that the benefits exceed those risks. The types of information that are provided to the agency for a new drug approval are extensive. They include a suite of animal, pharmacology, and toxicology tests, including extensive human clinical studies with many participants and over long duration.

The agency has a lot of tools in its portfolio for managing the risks in the approved drug context. They're in the labeling with detailed instructions on warnings on a drug package. Drugs can be limited to prescription only access and behind the counter. Risk evaluation and mitigation strategy can be developed through the Prevent Program. There can be DEA scheduling as needed, and there are robust systems for reporting adverse events.

So these are all part of the ecosystem through which the agency is able to manage risks related to drugs in the approved drug context.

Then moving on to dietary supplements, the

typical users are those seeking to supplement their diet and maintain their health. So this is again a subset of the population but this subset of the population is accessing dietary supplements voluntarily typically.

The safety standard for new dietary ingredients is for them to be reasonably expected to be safe. So this means that they really must be safe. However, benefits do not enter this equation. So any serious risks cannot be offset by any potential benefits or perceived benefits.

Typically what's provided in a premarket new dietary ingredient evaluation is there might be evidence of history of safe use. There typically is a safety narrative that builds a case for safety and there might be animal toxicology tests as needed.

There are options available in the dietary supplement pathway. Some examples include the safety standards that are in the narrative that are safe. Labeled conditions are used and help to manage certain risks. For instance, dietary supplements can be indicated for a limited consumption amount, a limited

duration of use and for a limited subset of the population, excluding vulnerable groups, for example, and the safety evaluation will take that into account, and again users can report adverse events and that can feed into the portfolio to manage risks.

Now, finally, for food ingredients, the typical user here is quite different. This is really the whole population, including vulnerable groups over their lifetime, and so this isn't something that people volunteer with.

The safety standard is reasonable certainty of no comment. So this is a strict safety standard that again does not include benefits. Common types of information provided are safety narrative and sometimes, as needed, animal toxicology tests, and in terms of risk management, this is primarily done to a very strict premarket safety standard and it doesn't take into account typically restricted conditions of use with arbitrary limitations on consumption or something like that.

So really the premarket strict safety standard is the primary way that food ingredients are

ensured that they're safe.

So just to conclude, I wanted to highlight some pathways for CBD that CBD has found in select foreign jurisdictions, starting with the European Union and the United Kingdom. In both of those jurisdictions, novel food pathway is the route that's been evaluated and because it was determined that CBD is a novel food jurisdiction, it was subject to those requirements.

As was noted earlier, the novel food evaluations going on in the European Union have just been put on hold for more data or new data as the scientists stated that they cannot currently establish the safety of CBD as a novel food due to data absent certainties about potential hazards related to CBD intake.

Australia and New Zealand have taken a different approach and CBD is available on the market but through a medicines pathway, not through food, and it's considered a pharmacist-only medicine. So this is widely comparable to the current accessibility of cannabis products in states through their state=

regulated medical cannabis programs.

And then Canada has a different approach, as well, where CBD products are accessible through their Cannabis Act and are subject to all of the rules and requirements that apply to cannabis under the Cannabis Act and so this case would be akin to an adult use regulated cannabis space. So they're going to be positioned alongside THC-rich cannabis products in Canada.

So that concludes my remarks and with that, I will turn it over to Dr. Cassandra Taylor to speak about the Drug Pathway.

MR. RAGHUWANSHI: Patrick, would you mind hitting Stop Share? Thank you.

Cassie, you're on mute.

DR. TAYLOR: Can you hear me now, Rakesh?

MR. RAGHUWANSHI: Loud and clear. Thanks.

DR. TAYLOR: Great. Thank you so much.

Good afternoon, everyone. Thank you for joining us today.

` My name is Cassie Taylor. I'm a chemist on the Botanical Review Team here in CDER. I'm in the

Office of Pharmaceutical Quality and today I'm going to talk to you about the Drug Regulation of Cannabis Products.

So as was mentioned previously, FDA regulates a wide variety of products and in this presentation, you will hear about the drug product regulations and there will be other presentations beyond this about other product categories.

So here at CDER we regulate prescription and non-prescription drugs and that includes generic drugs. We have a team-based review process which Dr. Woodcock had briefly mentioned earlier this morning. What that means is we have an independent and unbiased multi-disciplinary team of physicians, statisticians, chemists, pharmacologists, and other scientists who review investigators' data and proposed labeling.

Drugs are evaluated for safety, efficacy, and quality. If the review team establishes that a drug's health benefits outweigh its known risks, then CDER considers it safe enough to approve.

CDER works to ensure safe and effective drugs are available to improve the health of consumers. It

also ensures prescription and non-prescription drugs, both brand name and generic, work correctly and that the health benefits outweigh the known risks.

A brief overview of our drug authority will be provided here just so there's understanding for everyone on the Science Board.

So under the Food, Drug, and Cosmetic Act, the FD&C Act, any product, including a cannabis product, hemp or otherwise, that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or is an article, other than food, intended to affect the structure or any function of the body of man or other animals is considered to be a drug. With limited exceptions, a new drug must be approved by the FDA for its intended use before it may be introduced into interstate commerce.

FDA regulations can be found in Title 21 of the Code of Federal Regulations or 21 CFR.

Now here at CDER, we have premarket review. So this is the review that goes on prior to a drug being approved. Drugs include single molecule drugs as well as the TNF-alpha drugs. Sponsors, investigators,

researchers may utilize the regulatory pathway known as the Investigational New Drug Application or an IND. This is where drug development occurs.

Phases 1, 2, and 3 are conducted under an IND. Once the sponsor investigator reaches the end of Phase 3, they may decide to apply for a marketing application. The marketing application is known as the New Drug Application or an NDA.

Once an NDA is approved and on the market, CDER has post-market surveillance. This occurs in the safety of monitoring not just NDAs but Abbreviated New Drug Applications or ANDAs and prior to being approved as Biologic License Applications or BLAs. This is all done under the PHS Act.

We monitor products that reference under Section 3075 of the 21st Century CURES Act, but we also monitor products beyond the 21st Century CURES Act requirements.

So in a nutshell, we monitor the safety of all products that are identified in FDA's Adverse Event Reporting System or the FAERS Database.

For the botanical drug products, which is

where my team works on the Botanical Review Team, a botanical drug is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in humans. A botanical drug product consists of vegetable materials which may include plant materials, algae, macroscopic fungi, or combinations thereof, and a botanical drug will usually be available as but not limited to a solution. An example would be a tea, a powder, a tablet, a capsule, an elixir, a topical, or even an induction.

Botanical drug products often have unique features. So, for example, these are heterogeneous, very complex mixtures, as Dr. Woodcock was mentioning earlier. They often lack a distinct active ingredient and sometimes there's substantial prior cumulus.

Fermentation products and highly-purified or chemically-modified botanical substances are not considered botanical drug products.

The botanical drug specialty requires consideration and adjustment during our FDA team-based review process. So we have botanical drug development guidance for industry that was issued by CDER back in

2016. Within that guidance you will see all these considerations taken into account and it helps to facilitate the development of new therapies that are using botanical sources, not just cannabis but any botanical source.

There are compounds that are derived from and related to cannabis. So for those of you who have looked at our website, FDA Cannabis Research and Drug Approval Process, you will have seen the visual like this. In the middle you'll see Cannabis is defined as cannabis sativa which is a plant that contains over 80 different naturally-occurring compounds.

The main compounds that most of you are familiar with are called cannabinoids. We've heard about CBD and THC because they are the most well known, but plants are grown to produce varying concentrations of cannabinoids.

CBD and THC are two of those cannabinoids, but there are also over 100 others, and as humans start to intervene into any plant-growing process, these variations are created for these different compounds to express either more or less and so when humans

intervene to cultivate a plant, those variations are called cultivars.

This occurs in more than just cannabis. You see it often in all the different roses and tomatoes that are readily available to you. Those are all different cultivars.

If we look to the right of the diagram, we see the term "cannabis-related compounds." These are synthetic compounds that are created in the laboratory. They can be used to manufacture drug products. Some of the synthetic compounds may also occur naturally in the plant and others may not.

So one example of the synthetically-derived cannabinol is also naturally occurring. In contrast, nabilone does not occur naturally. The aqency has approved three synthetic cannabis-related drug products, Marinol citrus, also known as dronabinol, and Cesamet, known as nabilone.

On the left-hand side, you'll see the cannabis-derived compounds. These are compounds that occur naturally in the plant. So we're using CBD and THC as our example. These compounds are extracted

directly from the cannabis plant itself. They can be used to manufacture drug products, also, and one example is the highly-purified CBD that was extracted from a plant.

The agency approved one cannabis dry drug product, Epidiolex, also known as cannabidiol.

So let's dig a little bit deeper. We know that CBD and Delta and THC are very closely related in structure. You can see that in the red oval. But they're not the only compounds that are in cannabis. There are over 100 cannabinoids that occur naturally in cannabis.

Cannabinoids are unique to the cannabis plant. However, most of these have unknown safety profiles. Also, it's important to understand that the cannabis plant itself, when it's growing in the ground, the majority of these compounds exist in the acidic form. So if we take CBD as an example, that's the neutral molecule, where CBDA or cannabidiolic acid is actually what occurs in the plant itself.

In order for CBDA to become CBD, it has to undergo a chemical process known as decarboxylation.

That generally occurs when the plant is cut and harvested and blown dry. That heating is what actually helps to help the decarboxylation to occur and this occurs for other acid forms of the plant that are prominent in the natural plant itself that have to be decarboylated to form the neutral compounds.

Now in addition to cannabinoids, there are also a class of compounds known as Terpies. These are the aromatic compounds that you associate with the smell of cannabis, but many of the Terpies that are present in cannabis and there are over 100 that naturally occur in that compound are also found many other places throughout nature.

For example, when you peel an orange or you cut a lemon, you're used to that citrus smell. Limonene is generally the reason that you're smelling that citrus smell. If you have ever touched a pine tree, pining is the reason that you're smelling that smell and oftentimes there's more than one Terpy that's contributing to those smells, but, in general, this is the class of compound that is responsible for those aromatics that you're accompanied with, but the

terpenes are not unique to cannabis while the cannabinoids are.

In terms of cannabis drug development, we mentioned already that there's four products that are approved by FDA. There has also been some rescheduling of drug control actions upon approval.

Here is the Ergonomic Controlled Substance staff or CSS whose mission is to promote the public health through the medical science-based assessment and management of drug-release risks.

CSS performs specific functional roles, such as activities regarding the drug scheduling, abuse, and dependence, including international drug scheduling and control.

This role is the Department of HHS function under the CSA or the Controlled Substances Act, and it's delegated to the FDA and it is performed by the Controlled Substances staff within CDER.

CSS is responsible for writing the eight-factor analysis, scientific and medical assessments and drug recommendations to the DEA as required by the Department of Health and Human Services under the CSA.

The four food drug products that are on the screen here have all undergone an eight-factor analysis and scheduling recommendations were provided by CSS to HHS who then sends the recommendation to DEA. DEA takes the HHS recommendation into consideration for their scheduling decisions.

So here you'll see Marinol, also known as donabinol, approved in 1985, is scheduled to be under the Controlled Substances Act. For Cesamet or nabilone, also approved in 1985, is scheduled, too. Dronabinol approved in 2016 is scheduled, too. We have Epidiolex or CBD which is approved in 2018 for childhood seizures, and THC was originally scheduled but is now no longer controlled.

When we talk about drug development, we had discussed already the IND. Well, any cannabis product that's intended for use under clinical trial with a claim of therapy benefit for any disease claim is in fact a drug.

So the IND application, once it's submitted to the FDA and CDER receives it, the 30-day clock begins and by day 30, the integrated team that we had

talked about earlier will assess the information and make a determination if that IND is either safe to proceed or if there are clinical holds for a variety of safety reasons.

If you are not ready to submit an IND, you may request what's called a pre-IND meeting with the Clinical Division that is under the Therapeutic Research Area. So an example, if you were proposing to study an oncology drug, you would reach out to our Oncology Division in the Office of New Drugs and request a pre-IND meeting.

This allows sponsors and investigators the opportunity to get specific feedback on their particular drug product and then that will allow them to potentially submit an IND and will help them get to a safe to proceed and do their work.

Now once you complete your phases of drug development, the IND phase, the sponsors can then formally propose the FDA approve the new pharmaceutical under the New Drug Application or an NDA. In general, when drugs are studied under a clinical trial, cannabis drug, cannabis and cannabis drug compounds, just like

any other drug, you have to meet all the FDA requirements that are in the IND application.

So this includes three broad areas: animal pharmacology and toxicology studies, so these are our non-clinical studies. This is where our toxicologists and our pharmacologists really shine. The manufacturing information. Here, this is where you would submit your botanical raw material control where my team, the BRT, would review it, and you submit all your drug substance and drug product controls and the chemistry manufacturing controls where my CMC colleagues would review the drug substance and the drug product.

And then the third would e the clinical protocols and investigational information and so inclusion/exclusion criteria, informed consent, as well as information to confirm that the medical professionals are properly licensed to ensure safety.

Now for those who are wishing to look into how to submit an IND, we have an excellent draft guidance here that's labeled Investigation of New Drug Applications Prepared and Submitted by Sponsors and

Investigators. It's important to understand that in each phase of the clinical investigations, sponsors must submit sufficient information to ensure the identity, quality, purity, and potency or strength of the investigational drug. The amount of information appropriate to meet this expectation will increase the successive stages of drug development.

So that means the information needed in Phase 1 will not be the same as the information needed in Phase 3. It will be increased as you move through those stages of development.

And we treat products that contain cannabis or cannabis-derived compounds as we do any other FDA-regulated product. What does that mean? That means it's subject to the same authorities and requirements as FDA-regulated products containing any other substance.

We do have some information that is available to help sponsor investigators. So we have the Botanical Drug Development Guidance for industry that provides our current thinking on botanical drug development, the focus on the botanical quality

controls and the raw material growing conditions, but after the 2018 Farm Bill, many folks started reaching out to us for resources and so July 21st of 2020, FDA published the Draft Cannabis and Cannabis Drug Compounds Quality Considerations for Clinical Research and that document is a collaboration amongst CDER and we have put together the information that will help sponsors and investigators to conduct these types of trials.

Now when it comes to therapy research areas, over the last 15 years CDER has received over 800 INDs that have been submitted. In the first 40 years FDA received over 400 submissions for cannabis and cannabis-derived products.

However, in the last 10 years we have received nearly the same amount, 400 submissions. So that's a dramatic increase in submissions and we have nearly a 150 active findings right now.

So the example of research areas where these INDs are at is addiction and pain medicine, neurology, immunology and inflammation, as well as psychiatry.

CDER has a well-defined role to play in the

regulation and development of new drug products containing cannabis and cannabis-derived compounds and will continue to protect and promote and public health with respect to these products. CDER continues to focus on supporting scientific and rigorous testing and approval of human drugs derived from cannabis and supporting robust scientific research into understanding human and animal uses and safety of non-drug cannabis products.

FDA is committed to promote and protect the public health with respect to human drug products containing cannabis and cannabis-derived compounds, including enforcement action when needed.

Thank you very much and I'll hand it over to Dr. Noonan.

DR. NOONAN: Thanks, Dr. Taylor.

Good afternoon, everyone. My name's Greg Noonan. I am currently the Acting Deputy Director for the Office of Dietary Supplement Programs.

So as Dr. Taylor just gave us a great breakdown of the drug regulatory scheme, we're now going to move over into foods and I'm going to focus

specifically on dietary supplements and you'll hear from me today, and I'll remind you again and again because I think it's really important that dietary supplements are regulated as foods, not just important from a regulatory or a legal perspective, but it's also important from factor and sort of how the products are used and even the sort of intrinsic perceptions of safety that goes along with those.

Before I jump into the safety standards associated with dietary supplements, and really I use the plural there specifically because it is actually multiple standards, depending on the timing and the ingredient that we're talking about, here in this first slide I'm going to touch a little bit on the history, the market, and sort of the consumer uses because I'm hoping that that information will actually give the Science Board some context and perspective about answering the questions that Dr. Musser will discuss later on today.

So to show you the Dietary Supplement Health and Education Act was enacted in 1994, it defined the term "dietary supplement," and this is the first time

that that term was defined within the regulation. It also said that dietary supplement must contain a dietary ingredient. It must be for ingestion, and it also had added the exclusion clause, the idea of a new drug or a drug that's undergone substantial IND cannot be a dietary supplement.

Specialty dietary substance may not claim to diagnose, mitigate, treat, cure, prevent a disease. This is something that Dr. Cournoyer touched on in his table. We don't talk about the efficacy or the benefits when doing our safety assessments with dietary supplements.

It also established the requirements for the term "new dietary ingredients," and the new dietary ingredient is any ingredient that wasn't marketed in food prior to 1994.

I want to dig down into a little bit later. It's not that they actually represent a majority of the marketplace, but there at one point the FDA had the chance to review some safety and identity information. I think it's a good example that we can draw on and, finally, as I said, you're going to hear this a number

of times today, dietary supplements are regulated as a category of food.

If we go to the next slide, there were actually some findings in DSHEA that really give some idea of maybe what Congress was thinking about and at the time of DSHEA almost 50 percent of Americans were regularly consuming dietary supplements. These were generally vitamins, minerals, hebs, some amino acids, with vitamins and minerals being sort of the majority of that market.

The products were used to supplement the diet or supplement nutrition, to maintain health, maintain a healthy lifestyle, to reduce chronic disease.

I think one of the other interesting findings, I don't have it listed here, is the idea that people who took dietary supplements actually took on other aspects of healthy lifestyles, such as exercise. So it was a very holistic approach.

The market was actually relatively small. It was estimated about 600 supplement manufacturers and about 4,000 products and just maybe for some context, the market size is about $4 billion, I believe it was

estimated in '94, which is roughly the size of just the CBD market.

So in the next slide, if we take a look at what's happened in the nearly 30 years since DSHEA was passed. There's been a change both in consumer usage and in the marketplace. So currently estimates about 75 to 80 percent of Americans consume some dietary supplement with a majority of children, just over 50 percent of children being a part of that.

Vitamins and minerals are still the most common supplement that's used, but there has been this increase in sort of the targeted intended use and what I mean by that, things such as improved sleep and increased energy, so weight loss and reduced stress.

Now this trend has occurred over this nearly 30 years, but the last two years of the pandemic, there's been a dramatic or substantial increase in this intended use with things, such as reducing stress, taking on a larger portion of the market.

Speaking of the market, current estimates have it between 50 to 80,000 different products, so roughly 10 times the size, a little bit more, than it

was in 1994.

Not only is it bigger but there's a greater diversity not just in the products but also in the supply chain diversity that occurs, and again going back to this intended use, there has been a change in the standardized and specialty formulas, purified components, with more specific uses are something that has occurred.

As we move to the next slide, we've seen the sort of change in the market and this reflects somewhat the FDA's role in regulating supplements and how that may change, depending on the ingredient we're talking about.

So again dietary supplements are regulated as food and FDA does not approve any dietary supplement product. In fact, for ingredients marketed prior to 1994, I'll refer to them as pre-DSHEA ingredients, there is no premarket review required. So the FDA did not get safety or identity information about those products.

Focusing on the new dietary ingredients, again these were ones that were not on the market prior

to 1994. There's actually sort of two categories here. I'd like to split them out into (1) this idea of a new dietary ingredient that is already in the food supply. In that case, there is no premarket review. So they are very similar in the pre-DSHEA ingredients.

So the only chance that FDA has an opportunity to review ingredients that are going into supplements is the premarket review for NDIs that are not currently present in the food supply and I don't want to get into too much detail. Hopefully this works.

The interesting thing about that premarket review, so if a notifier comes forward and submits a notification for ingredient X, that does not cover every ingredient X product that is out there. It covers their product that contains ingredient X.

However, at that point the burden falls on the FDA to show that all those other products are actually not the same as the product that we have in review. So that burden falls to us and can be difficult without the initial data.

So if we go to the next slide, we can take a

look at how these different ingredients sort of fall into the different safety standards that we have. So for pre-DSHEA ingredient, our safety standards, our approach is all post=market. These are things that are all on the market and the burden's on the FDA to show that that ingredient, that product would cause a significant or unreasonable risk of illness or injury under recommended or ordinary conditions of use, a fairly high bar to reach. We need the data in order to demonstrate that.

For NDIs that have not been on the market, we have a premarket review and in that case, the reasonable expectation of safety under recommended conditions of use should be assessed and shown by the notifier.

In both of these, I want to sort of point to this conditions of use. We follow the labeled conditions of use. So whether it's intermittent or chronic, whether there are any warnings or a set of population, it's what's labeled or intended there, and the expectation is that the consumer follows those label indications.

The final one gets a little confusing. It's sort of a double negative here. I get caught up on this occasionally, the post-market NDI. So this idea that we have an ingredient that should be an NDI that is already on the market.

The burden is on the FDA to show that we have inadequate information to provide reasonable assurance it does not present a significant or unreasonable risk of illness or injury.

So if we have no information about it, that's something that we can sort of enforce on that safety standard. This ingredient X example I used, again the burden is on us to show that ingredient X from one source or location or manufacturer is different from the other.

So I want to dig down again into this premarket NDI. We move to the next slide. I really want to emphasize here again this is not the majority of the market, but it is the one chance that FDA has to review identity and safety information on products that are going to market.

So DSHEA lays out that manufacturers and

distributors must submit a notification to the FDA 75 days prior to introducing a new dietary ingredient to market. This is a notification. So this is the notifier's information and the notifier's safety assessment and determination and it's on the FDA's review of that information.

The NDI notification, one requirement is that it must meet what's laid out in 21 CFR 19.6 to be considered complete. I'll go into that in just a moment. But I think it's really important, this final point, that this is not an approval by the FDA.

In fact, even if the FDA identifies identity or safety concerns in our review, the product can still go to market and then the FDA bears the burden to demonstrate its adulterated.

We move to the next slide to talk a little bit about the requirements and so while I've cut the text down from 190.6 to make it presentable on a slide, really the type of information that is required is all captured here on this one slide.

So we need to know about the name and address of the manufacturer, the name and the description of

the new dietary ingredient, the description of the product or the dietary supplement that that ingredient may be in, the level of the new dietary ingredient, again the conditions of use, and, finally, the history of use or other evidence of safety, and this is really an important point that I'm going to spend a few more slides on.

So go to the next slide and talk about this identity portion first. We always sort of capture these. We call them different buckets, but they're actually two buckets that are connected because you need to understand the identity of your ingredient before you can really help establish the safety.

So in the identity portions, we ask for the description of the NDI, the description of the evidence verifying that you actually have figured out what the NDI is, and then some information on the manufacturing, and these are just some examples, information about the raw material. Often we will ask questions or ask for information about farming techniques, if those techniques may lead to a different ingredient, formulation ingredients, the manufacturing process,

specifications and the methods of analysis that are used to look at those specifications.

It's really a breakdown of what's your ingredient and how do you know that's actually the product ingredient that you're producing each time you manufacture.

This is the identity portion which then leads into the safety and again I want to emphasize here that the safety standard is laid out in 190.6, that the notification must contain history of use or other evidence of safety establishing that the NDI when used under the conditions recommended or suggested in the labeling of dietary supplement will reasonably be expected to be safe.

So I want to dive down into the history of uses of a really important point, especially related to dietary supplements. So if we go to the next slide, this is really the, I think to me, one of the options of having dietary supplements regulated as food.

This idea that these ingredients have been in the food supply or at least historically used for some time by perhaps large portions of the population. So

when we get history of use safety assessments, we really need a description and a characterization and it's really important here that that comparison compares and contrasts how the historically-consumed material is the same or different than the NDI.

Very often historically-consumed material may be a leaf or a root that's chewed while the NDI might be a reflection, some purification or extract. So how are those two things compared?

The exposure estimates. How does that exposure estimate perhaps from the unconcentrated form related to the exposure estimate that comes from the use of the new dietary ingredient perhaps in a more concentrated or a different form? These are all important things in a history of use.

The size and characteristics of the consuming population. Does that data exclude children that you have on historical use or does it exclude pregnant or women who may become pregnant? Those are very important considerations in that safety assessment.

Finally, we do ask for adverse events associated with the historically-consumed material. I

wouldn't say that the lack of an adverse event proves safety, but it's important to have that sort of context of information.

So a sufficient history of use can actually lead to a reasonable expectation of safety being established and with the number of notifications we get in, I'd say between five and 10 percent are the safety assessment or the expectation of safety is based solely on the history of use.

But when I say sufficient, it can be case-by-case. It depends on the ingredient, depends on how the conditions of use, but for the most part we're not talking about months or even simply years of historical data. We're usually looking into the sort of decades time frame. Long-term history of use is what really supports this sort of safety assessment.

Now there is the other reasonable evidence of safety. I'm going to talk about some of it in my next couple of slides.

So, in general, there are a variety of different studies that can be done. I mentioned in vitro studies. Generally, these cannot in themselves

establish safety, but they do support other studies. They may support a study in animal, how to perform an animal study or what clinical studies should be done, give us information that sort of helps guide the rest of safety assessments.

Animal studies, the specific recommended study depends very much on the conditions of use and the product. I'll talk about that a little bit in just the next slide, but I want to touch here on clinical studies because I think when I hear clinical studies when I first started in this area, I think very much, my mind goes to the sort of drug realm.

The clinical studies here are different. We are establishing safety. We are not establishing efficacy. I think even more importantly, these generally should be performed on healthy populations. A dietary supplement is not used to treat, mitigate, or cure a disease. It's used in a more widely general population and that's where those clinical studies really we gain power and safety data from that.

In the next slide, we'll dig down a little bit more into these. So the design of these additional

studies are really based on the ingredient and the product use. I can spend probably or a toxicologist could probably spend hours and hours talking about this, but I just want to touch on it briefly.

So the conditions of use, things such as the serving size, the target population, really helps to inform which animal and which clinical studies should be done.

The identity, the source of that material helps inform some of the animal studies or perhaps those in vitro studies that should be done.

Specifically here, the type of extract will influence what co-extractives come across into that purification system and so if there are possibly toxic signals from some of those co-extractives, those are particular studies that probably should be followed on in order to do a thorough safety assessment.

Ideally, studies should be performed on the product of commerce. Often when they are not, a real in-depth discussion of how the NDI or how the product or the article used in the animal studies or the clinical studies, how does it differ or how is it the

same from the product of commerce? That's really important to see if those studies can actually be applied to the product.

Finally, the safety narrative, and this is really the core of summarizing the data that the notifier used to establish that their product would be reasonably expected to be safe.

I often when we talk to notifiers, I often say they need to tell us a story in that summary of data, sort of pull all the data you have together and lay out that story of how you came to the decision of the reasonable expectations of safety.

So in closing, my final slide, just if I've done anything, hopefully you'll have a couple take-aways. First and foremost, and I'm sorry you've heard this many times but I'm going to say it again, dietary supplements are regulated as food. That's again not just a legal or a regulatory perspective but has context in how consumers view these products and how they use these products.

There are no approvals for dietary supplements in order to enter the market and while we

do have premarket reviews, that is only on a limited number or a limited set of new dietary ingredients or products from new dietary ingredients.

And while I've laid out some general and we do have specific safety study recommendations, none of these are requirements. Again, this is a notification and it is really a review of the notifier's determinations and information.

And with that, I will turn it over to the next speaker. Thank you.

DR. COURNOYER: Okay. Thank you.

So with that, I will wear my other hat in my capacity as a regulatory scientist at the Office of Food Additive Safety and one of the roles of the Office of Food Additive Safety is to regulate and evaluate the safety of food ingredients and so I'll give you a broad overview of the considerations that go into that, starting with what we regulate in terms of definitions.

Food additives require approval by the Office of Food Additive Safety and so what is a food additive? It's defined really broadly and it's any substance intended to be used and which results in it becoming

part of a food or otherwise affecting the characteristics of any food.

So that's quite broad, but there are some important exceptions and one of those being substances of use is generally recognized as safe. So something that becomes a part of food is a food additive unless it is generally recognized among qualified experts to be safe under the conditions of its intended use.

And so this provision was put in there because the approval of a food additive can be a resource-intensive effort and there are a lot of things that are added to food, a lot of which one would acknowledge is safe by general consensus, and so to avoid the resource burden of having to approve a really, really large number of things that are added to food, this provision was added to allow safety to be established rather than by the FDA by general consensus among experts.

So as I mentioned, food additives require premarket FDA review and approval which is done by petitioning the agency and that results in a regulation that stipulates how that food additive can be used.

On the other hand, if something is generally recognized as safe, the FDA approval is not required. We have a program where we evaluate the information behind the GRAS and we recognize the safe conclusion. This program is voluntary, but I will note that the standards and the requirements that apply to those ingredients, including the safety requirements, those are mandatory.

So GRAS is in fact a high standard, generally recognized as safe or referred to as GRAS. So it has two big elements. One is the evidence of safety. For something to be GRAS, it must be safe, and in fact the safety standard for a food additive that's approved by the agency or GRAS which isn't is the same. It's the same as a safety standard, but it has this added element of the general recognition part of it.

In order for something to be GRAS, the safety evidence, the key safety evidence must be reflecting of scientific consensus of experts and that information must also be generally available. So if the data is secret, it wouldn't work for GRAS. It has to be published and accepted in things like journals,

textbooks, scientific reports, or by authoritative bodies or something like that. So it's really two key pieces.

An example of something that is a food additive, aspartame, this was approved by the agency a long time ago because at the time it was new. Things that are typical and generally recognized as safe might be -- things that are made up of substances that are common parts of the food supply. Let's say things like proteins, carbohydrates, and organs.

However, I do want to note that just because something is a defined chemical, like aspartame, doesn't mean it cannot be generally recognized as safe. It's just that the science has to be very settled and the information needs to be in the public domain and one can point to the fact that it reflects scientific consensus. So today aspartame perhaps could be GRAS. So it's time to end it.

So what is the safety standard that applied to both these cases? It is reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use.

So this is a fairly high bar and it typically needs to account for expected use by the general population rather than picking and choosing which subparts of the population will be using it, including certain vulnerable groups, like the young, the elderly, and those who are pregnant. It typically needs to account for lifetime consumption and normally won't depend on special labels saying don't eat this if you, you know, have this condition or that.

Also, the safety standard, similar to dietary supplement ingredients, does not consider benefits and so if there is a risk, a potential benefit of something or perceived benefit of something can't offset it.

So the basic elements of a safety assessment for a food ingredient, one of the elements is what is it? As Dr. Noonan mentioned, an important initial element of a safety evaluation will be what is it in terms of its identity, its composition, how it's made, limits on certain impurities and contaminants, how is it going to be used.

Oftentimes with food ingredients, there's a technical effect or purpose for it to be added, like an

emulsifier or a preservative or a flavoring, where it's supposed to be used in terms of which types of food, how much in each category of food it will be used, and then an estimate needs to be done of how much are people expected to consume, and then, finally, is that amount of consumption going to be safe and data needs to support safety at the levels that people will be expected to consume.

So I'll get into those last two elements in the next slides.

So how much will people consume? This is something that's done as a matter of course in these types of safety assessments. So the first step is defining which type of food it's going to be used in, defining how much it's going to be used in each of those food types, and then estimates can be derived of the consumption of the foods that will contain the substance.

There are actually extensive databases that document how much of what people eat and these can be used to generate predictions of how much of a substance people will eat.

However, people all differ and some groups can consume more of certain foods than others and so there are ways of accounting for variation and for finding out what high-end consumers will use, right, because if it's safe for the average person but not for, let's say, the 90th percentile of user, then it's really not safe.

And then finally, there are ways of calculating how much of the substance people will be eating and it's typically expressed in a unit like milligrams per kilogram body weight per day. This not only needs to include the intended use of the substance but also background exposure from other sources.

So we get into a little more about how we determine whether exposure is safe. I first want to note that safety assessments really depend on the nature of the substance. So a thing that's a carbohydrate or a fat will have a different outcome than a small molecule in a food chemical.

So moving on, one of the key elements of a classical food chemical safety assessment is what's called a no observed adverse red flag or a NOEL and

this is the highest dose in an appropriately designed animal study that's been shown to cause no adverse effects.

But how the study is designed is extremely important. The study needs to assess the most sensitive toxicological endpoint for that substance and that means the organ system or the process that is most sensitive to that substance and the first thing that's likely to show harm.

Also, the study must use an appropriate model system, and I'll add that this approach tends to be useful for defined chemicals that are consumed in relatively small amounts. In this way, the test animals can be given exaggerated doses and that can be used to explore the toxicological profile. It's less applicable to macro ingredients, like fats, oils, carbohydrates, proteins, things like that.

Now moving on to one of the key factors of the food chemical safety assessment and how this is managed is the application of protective safety factors, and the way that this works is that the level that's been shown to not cause harm in test animals, we

want to make sure that actual exposure levels in humans are much lower and that gives a buffer and a margin for safety.

So typically this will be a hundredfold. So what we're showing to not cause harm in an animal we'll want a hundredfold less exposure in humans to ensure safety and the hundredfold is a commonly-applied safety factor which accounts for differences between the test animals and people and for differences between individuals.

If there are red flags in terms of safety or particularly problematic safety endpoints that showed up in the animal studies or if there are data gaps, additional safety factors can be applied to manage those risks and provide additional protection.

So finally, when a known level is divided by the protective safety factor, that produces an acceptable daily intake and the key is making sure that actual intake is below that and what that is is the amount of a substance that can be consumed daily over a lifetime with reasonable certainty and so again the proposed use of a substance can be considered safe if

the actual daily intake or estimated daily intake is less than the acceptable daily intake.

Both of these numbers, as I described how they're developed, they both entail some conservativeness to help ensure safety, right. So the estimated daily intake will be a highball estimate. The acceptable daily intake will be a low estimate, but the purpose of that is to ensure safety and meeting the safety strict standard.

I will also add you didn't hear me talk about human studies in this approach because they're typically not used in food chemical safety assessments and that's for several reasons.

One is that animal studies enable higher dosing and lifetime exposure and exposure during a reasonable time frame. So the higher dosing allows the discovery of potential endpoints or issues that you might not see in a human given a low amount.

Also, animals can be examined more thoroughly. They can be dissected. So this can reveal adverse effects that may not present in the human population. There are ethical concerns there, as well.

Human studies are typically only advised when there is a very specific question that can be addressed through a human study but it's not typical.

This whole approach is described in FDA's what's called the Red Book Guidance for Toxicity Studies for Food Ingredients.

So now shifting gears and related to that, we have evaluated three food ingredients for human food use through the GRAS Notice Program or Notification Program and these were for Hemp Seed, Hemp Seed Protein Powder, and Hemp Seed Oil, and as I referred to before, -- I'm sorry -- my audio is going in and out. I'm sorry about that. I think it has something to do with my bandwidth issues here. Have things gotten better? I don't want to proceed if no one can hear.

DR. KOWALCYK: We can hear you, Patrick. It's just going in and out a bit.

DR. COURNOYER: Oh, I see. All right. I'll keep my head still if that affects things. Sorry about that.

So as I mentioned, hemp seeds consist primarily of fat, protein, fiber, and carbohydrates,

and so that really makes them not too well suited to animal feeding studies and so the safety narrative provided by the notifier was discussing the safety of the fatty acid profile, the safety of the protein content, anti-nutrient levels in the seeds which are comparable to nuts and other seeds, information about the contamination levels of CBD and THC which are not present in the seed material itself but some can appear in the seeds due to cross-contamination.

It included some history of safe consumption for hemp seeds, but that's typically not a very big aspect of food ingredient safety assessment. Usually it takes a scientific approach.

We issued a constituent update describing our evaluation of these three GRAS notices, and, finally, we issued warning letters to companies selling foods with added CBD because we could not conclude that, as we stated in those warning letters, we could not conclude that CBD is generally recognized as safe among qualified experts for use in food and with that, we described some of the safety concerns that we have.

My colleague, Dr. Jeremy Gingrich, will

discuss those in more detail in the next presentation, and we stated that CBD is an unapproved food additive and therefore the food is adulterated.

We also issued warning letters to companies illegally selling Delta-8 THC added to food because it likewise in those products could not conclude that it was generally recognized as safe.

And finally, very recently, we warned consumers about accidental ingestion of food containing THC, particularly those products that resemble foods that don't contain THC and the risk of accidental consumption and there have been cases of this reported in the media and have shown up in adverse event reports and notably some of these have affected pediatric patients. So this is something that's very concerning and we wanted to make that clear to the public.

So thank you for your attention and with that we'll move on to the next speaker, Dr. Jeremy Gingrich.

DR. KOWALCYK: Excuse me. Before we go on to the next speaker, I think it might be advisable for us to take a 10-minute break. It's been an hour and a half since lunch. So I'm sure all of us could use a

break.

So we will come back at 2:10 and pick up with Jeremy's talk then. Thank you.

(Recess.)

DR. KOWALCYK: So we'd like to continue with the next speaker. Jeremy?

DR. GINGRICH: Hi, good afternoon, everyone.

My name is Jeremy Gingrich. I'm a toxicologist at FDA's Food Safety and Applied Nutrition, Office of Food Additive Safety, in the Division of Food Ingredients.

Today, I'm really excited to be giving you all a brief overview of the toxicological profile of CBD from the food safety perspective.

Next slide, please. During the talk I'll be discussing what's known about CBD's role in the endo-cannabinoid system, its receptor-binding profile, toxicokinetic studies that look at absorption, distribution, metabolism, and excretion or ADME for CBD, and known safety concerns from CBD consumption with supporting data.

I'm also be touching on some of CBD's

mechanisms of toxicity, conclusions that can be drawn from these data, as well as briefly mentioning how CBD's toxicological profile doesn't necessarily stop at CBD itself.

Next slide. So as you've already heard, CBD is one of two of the most abundant pharmacologically-active agents produced by the plant cannabis sativa, the other being Delta-9 tetrahydrocannabinol or simply THC.

You can see that from both CBD and THC they're structurally similar but unlike THX, CBD doesn't appear to have psycho-active potential. However, both do have roles in modulating the endo-cannabinoid system in humans and animals.

Next slide, please. So the endo-cannabinoid system is comprised of two receptors, CB1 and CB2, which are expressed throughout the body but tend to be concentrated in certain tissues. CB1 is predominantly in the brain, endocrine, and reproductive tissues, whereas CB2 is predominantly in the GI tract, kidney, and lymphoid tissues.

There are two endogenous ligands for these

receptors, banimine or AEA, and 2=arachidonoylglycerol or 2-AG.

Next slide. And can you click three times here, please? So while AEA and 2-AG are capable of binding either receptor, under normal physiological conditions they tend to preferentially bind, AEA to CB1 and the 2-AG to CB2.

So for AEA after receptor-binding, it's transported via the fatty acid binding protein or FAP to the enzyme fatty acid amide hydrolase or FAAH for degradation, and then 2-AG is very similar, just utilizing a different enzyme, monoacylgylcerol or MAGL for degradation.

Click one time. And so while CBD doesn't bind directly to CB1 or CB2, it's able to prolong endo-cannabinoid signaling by inhibiting FAAB presentation and FAAH and MAGL activity.

You can go to the next slide, please. So as I just mentioned and from the previous figure, we can see that CBD doesn't classically bind with CB1 or CB2. It has quite a weak affinity for these receptors but it's been deemed negative alisteric modulator,

essentially being antagonistic to the CB1 or CB2 receptors.

So despite this, CBD has been shown to have affinity for other receptors, like the amyloid Type 1 receptor or TripE1 and like CB1 and CB2, it also has similar antagonistic properties for the D1-like dopamine receptor and two of the opioid receptors.

There's also an abundant amount of receptors that CBD has been shown in vitro to act upon or have a binding affinity for. All in all, this is quite a complex receptor interaction profile, suggesting that the toxicological outcomes that I'll be discussing a little bit later are also complicated and likely multi-factorial.

Next slide. You can click to the next one then, please. So from our human clinical trials, we have a good sense of the toxicokinetic profile of CBD. It has a fairly low boro-vio-availability of six percent which increases just about threefold when consumed concomitantly with a high fat diet and that preferentially distributes to adipose tissue which isn't really surprising because of its lipophilic

nature.

CBD has a relatively short half-life of one to two hours following a single oral administration or two to five days under a more chronic exposure scenario.

CBD is primarily excreted in the feces with a small percentage in the urine.

Next slide. CBD undergoes Phase 1 metabolism primarily by its cytochrome P450, 2C19, and 3A4, although others have been implicated, and Phase 2 metabolism primarily by UGT1A7, 1A9, and 2B7.

The 7-carboxy CBD is the predominant metabolite that's been detected in humans and ADME studies in other animals, namely rodents and dog, have demonstrated a similar toxicokinetic profile in terms of absorption, distribution, and elimination, but they have varying metabolite profiles where the 7-hydroxy CBD is the predominant metabolite.

So it's interesting to note that that 7-hydroxy metabolite has been demonstrated to be biologically active and we don't know whether this is the case or not for the 7-carboxy metabolite in humans.

Next slide. Now to the meat of the talk being the safety concerns that are raised from toxicology studies on CBD. So I ordered these from really least concerning to most striking in immune-toxicity.

Next slide. So the data on the immuno-toxicity of CBD is fairly scant and only has been observed in vitro, whereas CBD exposure causes cultured mouse T and D lymphocytes to decrease in their function and apoptose.

This was concluded to occur through oxidative stress secondary to a reduction in intracellular gluco-thione. We see similar effects in both physiologically-normal and cancerous cells.

Next slide. So the second concern is of hepatoxicity which is phrased in the safety data for pharmaceutical grade CBD marketed under the trade name Epidiolex.

Here, up to 20 percent of individuals with epilepsy that were enrolled in the trial had abnormally elevated liver enzymes and we see from recent data that this is also the case for healthy individuals which

removes the anti-epileptic drug use as a potential confounding factor in this outcome.

In animal models, we also see increased liver enzymes and hepato-cellular hypertrophy is a common histopathology finding.

The next slide, please. In a similar vein, CBD has been shown to inhibit multiple acetic P450 enzymes in vitro which suggests that CBD can interfere with metabolism of drugs that utilize these pathways. Of particular interest and to keep in mind for the next couple of slides is one of these SEP2C11 which is male-specific and involved in testosterone metabolism.

CBD has also been demonstrated to inhibit the function of two important drug efflux transporters, being breast cancer resistance protein or BCRP and permeability glycol protein or PGP, which both normally function in a protective manner to remove pharmaceuticals and zenobiotics away from blood tissue carriers.

Next slide, please. So the final safety concern which is on developmental and reproductive toxicity outcomes has some of the most convincing data

on some of the most sensitive endpoints.

In adult rodents that were given -- this was CBD exposure to males only. We see a reduction in fertility and an increase in pre- and post-natal mortality in the offspring that were sired by these males. Along with this, we also see a decrease in circulating testosterone. That was a common finding in both rats and mice.

Next slide, please. For gestational exposure in rodents, meaning that both the males and the females would have been exposed to CBD prior to mating and then the females continued their exposure throughout gestation and lactation.

So here we see that fewer live pups were born. The mothers had a shorter gestational length that resulted in smaller offspring. We also see that these male offspring have reduced testicular size and weight. This is even accounted for in their smaller size.

The abnormalities in testes were also accompanied by a decrease in viable sperm and reduced pregnancy success once those offspring reached sexual

maturity which is also developmentally delayed.

One study looked at neurobehavioral development and showed that female offspring that were exposed to CBD gestationally were more likely to show anxiety-like behaviors than their male counterparts later in life and then one study done in rabbits also reported perturbations and skeletal development.

Next slide, please. So of greater relevance to humans is a longer-term repeated dose toxicology study that was performed in Rhesus monkeys where adults of both sexes were given CBD daily for 90 days. All doses that were tested resulted in up to a 75 percent reduction in testes and ovary weights.

So this study included a wash-up period where after that 90 days of exposure, CBD use was discontinued for 30 days prior to tissue collection and in that case the testes weights remained depressed under those conditions and there was a significant decrease in spermatogenesis at all doses tested accompanying some morphological changes in the testes that occurred at higher doses.

Next slide, please. So importantly these

developments of reproductive toxicity outcomes following CBD exposure are observed not only in mammals but across evolutionary distinct organisms which suggests that it's likely to occur in humans, as well.

In chickens, we know CBD is embryo-toxic if exposure occurs in ovum. CBD has been shown to decrease the reproductive success of sea urchin by preventing chromosomal reaction that's necessary for egg fertilization, and in zebra fish, which are routinely used for high throughput screening of developmental toxicants, it presents a myriad of developmental abnormalities when exposed environmentally to CBD.

Next slide. So together these data point to six potential mechanisms of toxicity for CBD, including prolonged or erroneous endo-cannabinoid signaling, complex receptor-binding and activity profile. We have disturbances in testosterone homeostasis or steroidogenesis, disruption in normal liver enzyme expression R function, inhibition of normal drug transporter function, and oxidative stress.

Next slide, please. So we can conclude from

the studies that were discussed today that CBD has the potential to cause immune liver and/or developmental and reproductive toxicity in animals. I want to stress that with any of these outcomes the effects may not be immediately evident by the user.

For example, acute liver toxicity is often asymptomatic. So this effect could go unrecognized for a prolonged period of time in individuals who don't routinely have blood work done, and in the case of potential effects on the testes and spermatogenesis, this may only present as a sub-fertility in individuals trying to conceive a child and there would likely be a complete absence of any outwardly visible damage.

So these examples show how complicated post-marketing of CBD could be in the general population.

So because of these concerns, among others, FDA has issued warning letters to certain companies selling food products containing CBD stating that CBD is not generally recognized as safe or GRAS for either human or animal food use. I've included the links down here to the press announcement if you'd like to read

more.

So I've titled this last slide here Beyond CBD because I think it seems that the toxicological profile of CBD extends beyond CBD itself. Through a fairly simple chemical reaction, CBD can be converted into a slew of synthetic cannabinoids, as was mentioned a little earlier during the Public Comments, one of which being Delta-8 THC or just Delta-8, and Delta-8 has been shown to have a very similar, not identical, toxicological profile to THC or Delta-9 THC, especially in regard to its psycho-active potential.

We have begun seeing some of these synthetic cannabinoids pop up in commerce, some even in the food space. So I've also include a link here to an article that was published by FDA on the things you should know in regard to Delta-8 if you're interested in learning more.

Next slide. And I just wanted to acknowledge some others in my division, office, and center who helped organize some of these data for the presentation, and then a list of references which certainly isn't exhaustive but some of whose data I've

spoken on in this presentation.

With that, I'd like to thank you all for your time and pass the presentation on to Dr. Musser. Thank you.

DR. MUSSER: Okay. Thank you, everyone, and we are almost done. Just would like to conclude the conversation today with the questions, the specific questions we have for the Science Board.

I'd especially like to thank my FDA colleagues for the background they've given regarding our regulatory processes and the science used to evaluate the safety of these various substances and how they fit into their various regulatory schemes, whether it be food or drugs, and we'll progress now with I am also the Deputy Center Director for Scientific Operations at the Center for Food Safety and Applied Nutrition.

So the concluding remarks, I'd just like to start with a little bit of the background and frame things a little bit for the Science Board, having had a long day and I'm sure you're tired. I promise I will be quick here.

Just to reiterate, we'd like to have you consider substances that are consumed with the intent of experiencing a pharmacological often psycho-active effect and that there's really no other function of the product. In other words, consumers are seeking these products out not as a flavor or a nutrient or preservative but they're seeking them out for this specific component, and also the consumers might consume the amounts needed to cause the desired effect regardless of the serving or dosage recommended.

Second, I should note in regards to one, we're not talking about -- when we talk about pharmacological effects, we're not talking about the sort of common things like quinine and tonic water that's a flavor but also has some drug-like pharmacologic activity or cinnamon which contains coumarin. We're talking about a completely different pharmacologic effect, one where people are taking the product for that pharmacologic effect.

The substance is made relevant in the history of safe use and so just for context, people may have inhaled the product historically and now it's provided

in a myriad of products from cosmetic creams to sprays to inhalation to food to drinks and people would be confronted with a multitude of doses and approaches to consuming these products.

The third point I'd like you to consider is that society may prefer access over prohibition. In other words, they would like to have these products and they would not like to be prohibited from having them, although they do want a degree of oversight and safeguards.

So they would like someone overseeing the quality, safety, and purity of the standards and the approaches and the products that are marketed.

And then the fourth approach is, you know, the expected route for access to this outside of the drug pathway would be as a food or a dietary supplement and we'd like you to consider whether other pathways might exist similar to what would exist for tobacco or alcohol that we don't need to just have only one consideration of drug or dietary supplement food.

Next, please. So the first question we would like to have you consider relates to the scientific

safety assessment of these products. How might a public health agency assess the unique toxicologic safety questions raised by a substance or substances in this case likely used for pharmacological, in this case meaning psycho-active effects, outside the context of an approved drug, given where it would sit within the agency and what you've already heard about the way we would do safety evaluations in those other areas, especially in this case, if there is a lack of substantial history of safe use of consumers in the context of use.

So as I mentioned previously, if it was an inhaled product before and now it's available as a drink or, you know, a tablet or capsule, what does that mean in terms of a safety perspective?

Also, the ability for consumers to self-administer without practical limitations to dosage. So we have talked about the way we, as the agency, consider chronic as opposed to acute. So someone could take it for a month or two, not have any concerns from the acute approach, but if we consider in our safety evaluations that people take it for a lifetime and at a

high dose, our safety evaluation will indicate that a very, very low dose would be recommended, for example, and yet what consumers prepare is much, much higher than that.

So regardless of what's on the label, would they take higher and higher amounts, thereby limiting the practical approach of dosage labeling of the product?

The next slide, please. Okay. And so this is our second question and last question. The same scenarios, but in this case we're thinking about broadly how a public health authority might serve society and talk about the risk management in general. How would we manage exactly the approach we would take for risk? Is it the harm scenario? Is it a risk scenario? Is it some other management scenario if we had to manage these in a different way outside of the approaches we currently have or the tools we're currently using along with all the things that you've heard today?

And so with that, I hope that we have been clear, that the questions have been clear. I would

like to go to the final slide now.

So I'll turn it over to the Chair in just a moment, but first I'd like to thank the members of the Science Board for considering these questions. Although they're short, they're meaty and are going to require some significant thought and we really appreciate the time that you're going to spend looking into this for us and we look forward to the advice that you provide.

I'd also like to thank the public for their comments in advance of today's meeting and during the meeting. We very much appreciate the input that we've received so far.

So with that, I will turn it back over to Dr. Kowalcyk, the Chair.,

DR. KOWALCYK: Great. Thank you very much.

Patrick, you have your hand raised.

DR. COURNOYER: Yes, thank you. I just wanted to add a couple clarifying points.

You'll see in the questions here, and I'll keep these up on the slide, that we do mention the words "psycho-active," and by that we don't necessarily

mean to get high or cause a europhogenic effect. We're referring to psycho-active more broadly than that.

So as Dr. Woodcock pointed out earlier, some of the reasons people say they're using CBD relate to effects on the nervous system, and another point I wanted to re-emphasize, as well, is that we're not asking necessarily about specific regulatory pathways that exist. We've laid out the ones that we have.

As these questions are worded, they're worded very broadly to just speak about generally outside of the drug context. How do we tackle the Question 1, some of these safety assessment challenges, and then Question 2, just broadly, some off the risk management challenges?

Thank you.

DR. KOWALCYK: Okay. Thank you for that.

So now that we've heard the background and we've gotten literature and remarks from the public, I'd like to open this up to a discussion among the Science Board members and with the goal of trying to answer the questions posed before us.

So are there any comments or questions for

our presenters from FDA today? Please raise your hand and then I can recognize you. Dr. Tosi?

DR. TOSI: I want to thank the presenters. This has been spectacular.

Just to set the stage, by definition, I'm a pediatric orthopedic surgeon. I take care of folks with rare diseases. You know, my youngest kid's 60 in my clinic and I am very concerned about the use of cannabis and I urge you very much as you're thinking about all of your questions to go to the heart of the question or the issue for my patients which came up very early this morning, pain, chronic pain, and that we can discuss the toxicology till we're blue in the face.

If you're not tying in the pain and response to pain issue, anything you come up with is going to be ignored and that's just realistic.

A totally different issue, I was concerned that most of the data presented did not speak to the pediatric brain and on a personal level, as these questions were delineated, I think that's going to be very important from a regulatory or long-term legal

standpoint.

Thank you.

DR. KOWALCYK: Thank you.

Are there any further questions or comments on that, in response to that? Dr. Woodcock.

DR. WOODCOCK: Yes, we do have the ability to do neurocognitive toxicologic assessments, you know, gestational developmental neurocognitive assessments at our National Center for Neurotoxicologic Research. We're currently involved right now, I think they're doing some studies or going to start them to see which animals actually have similar metabolites to humans because we can do a lot of studies in animals that have different metabolites and if we don't understand the relative contribution of the different metabolites, those studies could be leading us astray, but we do have the capability to look at that and we did that, for example, when we were evaluating anesthesia in newborns and early development. It was very helpful.

DR. TOSI: Thank you. That work, I assume you know, really influenced surgeons like myself significantly in terms of really trying to limit the

anesthesias that we do.

DR. WOODCOCK: Yes, and I thank you. You know, when the people in Neuro Division came to me in 1999 and said we can't endorse a pediatric study with ketamine because of the oneo lesions in the brain, I said, well, we have to study this because it's being used all the time and similar agents. So thank you, yeah.

DR. TOSI: We're very grateful.

DR. KOWALCYK: Thank you.

Dr. Rye.

DR. RYU: Hi, this is so new, and my question is regarding the mechanism of toxicity, if I may.

At one point during the day, randomized to make sure the different metabolism or response to the CBD or cannabinoids, but according to the last presentation, it went toward the reproductive toxicity and mice showed similar responses.

So just wondering how such differences or similarities were driven and among six potential mechanisms, you know, proposed or speculated, how about oxidative stress in terms of interaction with xeno

antibiotics and, you know, drugs, if there has been, you know, addressed in a way that it could be, you know, going back to the toxicological mechanism of toxicity.

DR. GINGRICH: Do you want me to touch on that?

DR. KOWALCYK: Yes.

DR. GINGRICH: I guess I'll get at the first part of your question is how are the differences driven in metabolism.

My kneejerk reaction to that is that we're really unsure how they're driven. We know that the differences in metabolism could be what's responsible for some of the differences that we see, but part of it is we have the missing piece of the puzzle on the 7-carboxy CBD. We're not sure if that's active or not. So that's a black box and could account for -- you know, we already know that 7-hydroxy CBD is biologically active.

If we assume the same for 7-carboxy, then all of the results that are similar between human and animal studies become a little bit more relevant in

that light.

And then as far as oxidative stress and looking at how that might impact CBD's effect on producing oxidative stress in, I guess, the context of co-exposure with other xenobiotics, that's a great question.

I don't think -- to my knowledge, that's not been looked at, but yet that would be certainly interesting and something that can -- I can double-check on that for you, as well.

DR. RYU: Okay. Thank you very much.

DR. WOODCOCK: Can I ask another question?

DR. KOWALCYK: Yes, Dr. Woodcock.

DR. WOODCOCK: So I wanted to know, do you think the plan then to try to determine if we can find an animal species that has a similar metabolism to humans is a rational one, given this discussion you just had?

DR. GINGRICH: Well, I do. I think that there's multiple pathways that you can answer this same question for.

So whether we figure out if there's an animal

model that has better metabolism or we can determine that that carboxy metabolite is active or not, those would answer similar questions in my opinion.

DR. KOWALCYK: Okay. Dr. Afshari? Dr. Afshari, we cannot hear you.

DR. AFSHARI: Sorry about that. Can you hear me now?

DR. KOWALCYK: Yes, we can. Thanks.

DR. AFSHARI: Perfect. I just wanted to clarify. Are we supposed to be -- can we start to opine on these questions here or is this just to ask clarifying questions of the speakers we just heard in the last section?

DR. KOWALCYK: We can start to opine on the questions.

DR. AFSHARI: Okay.

DR. KOWALCYK: I did want to offer the opportunity. There were a lot of presentations there and everyone was a bit quiet. So you also have the opportunity to ask questions of the speakers if you'd like.

DR. AFSHARI: Thank you.

There was a lot there and I think a lot of really helpful information but also a lot of really good thinking and so I thought what I'll do is just kick off some ideas in terms of, you know, aspects of the framework that I think were also encompassed in many of the presentations, pulling it together and reflecting on it's probably helpful, and so I think, as I think about how we would approach this putting the hat on of a pharmacologist/toxicologist, you know, where I would start and we've heard today from a number of speakers is (1) determining the components that we have to measure.

I think for each of the pieces I'm going to bring up what's helpful and the opportunity for FDA is to provide a source of knowledge and a compendium available for, you know, whether it's researchers or it's regulators to start to bring the standards.

So there's obviously the analytical methods in determining the components in the various products and, you know, once you have those, then you could start to say we can determine the activities associated with those and, you know, we've heard today numerous

panels -- you know, I asked the question earlier around the CB1 receptor, but there's various binding and functional assays that can be done in the context of human receptors or other targets to broadly understand, you know, what are the targets of engagement, if you will, for these components.

I think the other aspects of the biology that should be considered then is once you know where these components may be interacting is understanding where those targets may be expressed and so expression doesn't mean you get toxicity. It doesn't mean you get activity, but it means it's possible if you're able to put that component, biochemical component with that target that you could get biology.

This is where I think again the unique aspect to pull across a lot of databases not only where do we think that target's expressed in, quote unquote, normal tissue but also in various disease states or age states and that data does continue to mature in the public domain.

I think once you have that picture then and again I'll get to --

DR. KOWALCYK: Dr. Afshari, we're losing you.

DR. AFSHARI: Oh, is it okay? Maybe I'll turn off my video. Maybe that'll help with the bandwidth.

I think the --

DR. KOWALCYK: Can others hear her?

DR. COURNOYER: I actually can hear her.

DR. AFSHARI: You can? You can? Okay. Maybe my headset is stopping. It's okay? Okay. All right.

DR. REISS: Yeah. We can hear her.

DR. AFSHARI: Okay. So in terms of in addition to the distribution and the expression of the target, you can start to glean a lot from various pharmacology compendia, genetic databases, and others what you might predict as activity if you would activate or inhibit the activity of those receptors, and all of these methods and approaches are something that we commonly use today when we look at various drug targets or various targets of toxicologic concern in various pieces. That's all relatively -- I'll say it's relatively simple, but it doesn't require animal

studies. It's all biochemical, molecular, and data-mining approaches.

You will have to spend some time, though, on this last topic we talked about which is understanding, you know, not only metabolism but distribution and elimination and I think I saw in some of the references you provided an aspect that's going to be of particular concern is if these compounds accumulate with frequent dose.

So when I look at the last question here, you know, without practical limitations to dosage, you know, if these compounds are distributing, you know, and accumulating, you know, that's going to be a particular -- you know, a different biology than what you're going to see in a short-term maybe in vitro assay or short-term in vivo study.

So I think there's a lot of framework that we can pull on from, you know, what the field of toxicology's done with mixtures, how we're thinking about novel targets, but it's going to really require pulling all of that in and then saying, okay, how do we address some of these questions but, in particular, the

psycho-active piece we all know is going to be challenging. The translation of those endpoints from in vitro or in vivo preclinical models to humans are not trivial and that's one that certainly I would say is a Science Board in particular around these products we would need to make sure we engage with experts in that area of research.

Thank you.

DR. KOWALCYK: My apologies. Tony, you had your hand up.

DR. BAHINSKI: Yes. Just following on with Cindy's comments, this is a question to Jeremy.

You know, reviewing the data, it didn't look like there's any, especially from the drug development studies, there wasn't any animal or human no adverse effect levels identified in any of the studies, especially for the liver, potential liver toxicity, is that correct? First of all, is that correct?

And then, second, if you wanted to look at -- and again those are probably much higher doses than you're going to see in food. Is there a way to utilize either in vitro methods or novel alternative methods

plus, you know, PB/PK modeling or some kind of in vitro/in vivo extrapolation to try and identify, you know, where you may see, you know, a lack of effect that correlates with, you know, human clinical plasma levels, other than potentially, you know, doing a study in the healthy volunteers at lower doses as a clinical study?

DR. GINGRICH: So for the no-L at least, there has not been one identified. We do have some data on the low-L. The European Food Safety Association also kind of -- they have stated an upper pragmatic limit that is also based off of a low-L.

So we can use some of that to, you know, determine a benchmark dose or even use the low-L and apply some additional safety factors to determine a dose that might be within some safe level or that may be considered to be no adverse effect, but it would be quite low based off of the current data that we have, and I also -- excuse me.

As hard as the tools that you described, I think those would be potentially useful in, you know, getting at -- they might be useful in the future for

kind of getting at some of these -- answering some of these questions, but standing alone, they might not be enough for us just having, you know, a series of new approach methodologies to get past some of the negative data that we already have. So that will be a hurdle.

DR. BAHINSKI: Yeah. And to Cindy's point, you know, again that would be more acute effects. You know, the chronic effects could be very different, especially with any accumulation or -- and there's wide variability, as you noted, with meals, fatty meals, you get much higher exposures than you would expect, in addition to potential drug-drug interactions.

DR. KOWALCYK: Thank you.

Dr. Sarwal?

DR. SARWAL: Yes, thank you.

Very interesting. I'm not an expert in any of this stuff, but I've been looking at it. Of course, I have children and I also manage pediatric patients and so I think this is an extremely important topic for all of us to get into further and just looking at it from really a bird's eye view, I can look at three large kind of use case scenarios and in those three

large use case scenarios, potentially we can try and develop some kind of a stratification method on how to understand the use of these agents in each of those scenarios with regards to safety and efficacy.

The way I look at it, there's three kind of use case scenarios, and Number 1 is the recreational use where I think our primary aspect there is safety with regards to again cumulative repeat dosing accommodation and maybe the issue of how do you actually get safety with regards to somebody driving under the influence or not and how do you actually measure that. I know that's a tall order, but I think if I were to look at it that's from a recreational point of view, you just want to make sure that there are safety aspects in place with use, with repeat use, but also with under the influence use when you're actually driving a vehicle and to me actually that part is not clear at all.

And there, one would assume, apart from the very frequent use or most of that use would be sporadic, and then there is the medicinal use, which to me is different from an outpatient point of view as

well as potentially getting to some of the more potent agents to go into an inpatient kind of use and maybe that would be increasingly used over time.

I think that the latter is going to be quite rare, but I think if we were to use it in that setting, we have a unique opportunity to learn with regards to drug-to-drug interaction with much closer monitoring, looking at more indices of multi-system toxicity, etcetera.

We could also look at the medicinal use in the middle zone which is at the outpatient level. Now these patients are outside the hospital, not as sick, but I think there that's probably our largest bulk of the population that we need to understand and so how do we look at things like the clinical confounders, such as body mass, ethnic variations, as well as, I think you already talked about this, interaction with foods, etcetera, which I expect is going to be more minor, but really evaluating are there wide swings in PK/PD variations that we should be putting a lot of effort into control or are these into very narrow wobble areas and so therefore putting an enormous amount of effort

into uncovering those and designing trials to uncover those may be counterproductive because that would just come out in the wash.

But I think again the big issue there is going to be again the effect of repeat use, higher dosing. Does accommodation occur so that higher and higher doses have to be used with repeated use, and then, of course, the big issue again is going to be drug interactions because a lot of these people may be on other psycho-actives or other agents?

So I know I'm just summarizing what's been beautifully said by many, but I was hoping that if we look at these three big buckets we can put guardrails around what are the things that we absolutely need to get data on and then start thinking about what's the best way to get the data. Is some of this already available through maybe some trials that are ongoing? How many healthy volunteer trials do we need to do and what kind of dose escalation or repeated dosing needs to be tracked?

So I think just summarizing again, it needs to be like what do we want to get out of this and which

are our critical patient populations and how do we triage what we want to address first, second, third because there are so many questions?

DR. KOWALCYK: Thank you.

Before I call Dr. Reiss, I just wanted to follow up and this was a question that I had while listening to the presentations, and I'm not an expert, I'm not a toxicologist here, but often when you cook food, it changes chemically. So you need to be -- I am concerned not just about the drug-drug interactions but also the interactions that may occur, the changes that may occur, I should say, as food is processed and/or cooked in some way.

So that's one of my concerns and, of course, if we look at this, particularly Bullet 3, variability in product quality and consumption and the concentration of active constituents, in food often things are not well mixed, right. So you can have a heterogeneous distribution of products throughout the food and so that, of course, is something that I'm concerned about, as well, but I did not hear anything in the presentations about that.

I apologize. If you can't tell already, I have a horrible cold today and my ears are quite full. So if I don't catch something, it's because of that.

But in any case, those were a couple of my thoughts that I thought I'd interject here before I called on Dr. Reiss.

DR. REISS: Good. Yes, so I'll maybe put a couple things on the table.

I understand, I think I understand the pickle that you find yourself in here, and the presentations were wonderful and really quite, quite very clear and very, very helpful.

This is being, you know, considered as a food, but yet it really has the characteristics -- I don't want to say it has characteristics. To me that's the wrong terminology.

But it seems to be closer to the drug side of things or the pharmacologic side, you know, if we consider that a whole spectrum and that things are chopped up for regulatory purposes and across that spectrum, and, you know, in evaluating the, you know, tolerability, the toxicity, you know, it's sounding

like it doesn't come close to your definition of safe, you know, as you've sort of outlined it in the presentations today. It's not harmful because I found, you know, sort of the slide listing that toxicity obviously is quite concerning.

The critical issue there that Dr. Woodcock brought up also and had a conversation about it is to the animal models predict human toxicity because of the differences in the metabolites and I'm assuming that the animal models don't have that carboxylic acid metabolite there.

So it's hard to know, but if there is and you have no effect level, you know, this would sort of be a compound and we're not thinking now about sort of the whole problem and issues of the quality of the product and the constituents of the product which lends another level of problem.

But if you have a no effect level, that's really sort of true and if this were a drug, we probably would stop development on this and move on to something else.

So to, you know, put that within the context

of a food, I think is going to be a little challenging and I think that's where your issues or concerns are about and so it does revolve around sort of understanding the animal toxicology models and the metabolism and so on and so forth, and if you've hit a wall that probably is important for the public to know.

DR. WOODCOCK: Could I?

DR. KOWALCYK: Yes, Dr. Woodcock.

DR. WOODCOCK: Thank you.

I'm sorry. I can't get to my hand button on this presentation for some reason.

So, you know, I think one of the issues is the usage data that I presented. It's out there and all these people are using it and, you know, we need to probably get as much information out as quickly as possible, leaving aside the regulatory issue, about what is this stuff doing to people.

Of course, we don't completely know yet, as we presented, but I think that's sort of the other issue in front of us, you know. You're looking at the fit to the regulatory regimes that we have, but, on the other hand, it's out there. People are using it and

our experience is, for example, in the nicotine world, if we put a regulatory regime on something, then this has all these molecules that are very similar, right, and like when we did that to tobacco products, to vaping, then the industry countered with synthetic nicotine which wasn't regulated until Congress intervened.

So here there's like this tremendous opportunity for all these different compounds and so I think we really appreciate all the advice on how we can get as much information as possible out there or generate as much scientific information as possible on the consequences of ingesting these things because people are doing all these things, including kids are getting into these CBD products because they're so ubiquitous.

DR. KOWALCYK: Yes. So, Dr. Noonan. I know, Dr. Nolan, I know you have your hand raised, but I saw Dr. Noonan. I didn't know if you were responding to Dr. Reiss' or you had a different comment.

DR. NOONAN: I was actually responding to your question about foods and accessibility. I don't

have any data for you right today or tomorrow, but it's actually along with the long-term, the short-term study data and the long-term study data, we do see great variability in what is in these products. We don't know if that's a problem with the starting material or something to do with stability.

So we are looking at the stability of a variety of cannabinoids in food. So that data will be forthcoming. Unfortunately, I can't provide it today or tomorrow, but I just wanted to say it's sort of on our list of things to continue to look at.

DR. KOWALCYK: Okay. Thank you.

Dr. Nolan.

DR. NOLAN: Thank you.

Once again, I'm struck by what an overwhelming task the FDA has. I mean, my gosh, what a huge topic this alone is, and, you know, the variability in what's available and the product quality composition, all the other aspects that have been mentioned by my colleagues here. It's just I keep coming back. How do you regulate it or is it something you can make the industry do and very narrowly draw a

path through labeling? Can you put the onus on the industry rather than on the agency?

DR. WOODCOCK: To regulate it, we have to determine it is a product subject to FDA regulation. We've already said something about putting it in foods, okay, and however, you know, we have to decide if it's subject to FDA regulation, through one of the pathways, we can't -- I mean, we have a couple of other pathways, like nicotine-containing products. That one is probably a better word and it's probably, you know, not a medical device.

So, you know, we have to decide if one of the pathways fit in order for us to take that kind of action that would be not, you know, to say, well, it's -- you can't have this product or whatever.

That's our problem is one of the presenters said there's a considerable desire, including, you know, through the Farm Bill to make these sorts of products available to people, but we saw the toxicologic profile and so you're right, it can be very bad, for example, whenever public presenters talk about compounds that were completely mislabeled and had

gigantic amounts of, you know, psycho-active product in them.

She was talking about cannabis primarily but the same thing could happen here, I would think.

DR. KOWALCYK: Thank you.

Dr. Boor?

DR. BOOR: Thank you.

And so sort of splitting the difference between what I had heard from Dr. Califf and what I'm hearing from Dr. Woodcock, Dr. Califf said this morning, he said there is no safe level for tobacco. I mean, he said that very clearly, and the data right now suggest that there is no safe level, at least as defined by regulation, as defined by science at this point.

So I am fully onboard with the fact that understanding mechanisms and understanding breakdown products and the food products and so forth is important and needs to happen, but in the short run, is it possible to require a label that says based on the science currently available, there is no safe level of consumption for products containing these compounds?

I mean, that way at least people have some information upon which to make a decision, and I don't have any idea about the legal status of something like that, and I can see Dr. Woodcock is responding. So I'll be quiet and see what she has to say.

DR. WOODCOCK: Well, tobacco has a regulatory regime and that regulatory regime is actually harm reduction. So society has decided it's okay for people to make the choice to expose themselves to nicotine products, but what we will try to do as a public health agency will try to mitigate the harm by making less, still toxic, but less toxic products available and hoping the market will go toward those products and diminish the amount of harm.

What we're saying here is we don't have a regulatory scheme like that for this type of product. We have the foods schemes that we're explaining in great detail or the drugs scheme and so that makes it, you know, we can't just sort of issue labels out of thin air. We have to have some kind of embodiment of a framework to it.

DR. KOWALCYK: Steve, did you have any

thoughts about that? You're muted.

DR. MUSSER: I was trying to describe this to one of my friends on vacation last week and I said it's like the round peg in the square hole or square peg in the round hole thing, except we have two holes. We have a square hole and a round hole, one for drugs, one for foods, and a hexagonal peg and it doesn't fit, and so, you know, we're left in kind of no man's land here with what the public wants, manufacturers want to produce, and what our regulatory authorities allow us to do.

DR. WOODCOCK: As I said, we're not asking you all to figure out a regulatory path for us. We're asking you to figure out or give us advice on what additional scientific steps we should do to figure out the toxicities of this product and related products. Thanks.

DR. KOWALCYK: That's a good reminder.

Dr. Rye.

DR. RYU: Thank you.

I would like how Dr. Musser put it this way. I mean, this would be more toward the tobacco or the

alcohol categories, but right now if you're going to ask whether we could put it in the food or dietary supplement category instead of drug, but I guess, you know, there's going to be an argument whether it could either be food ingredient versus dietary supplement, pros and cons, plus and minuses, but at the least I think we would go with this quality control or the composition or the variability of the concentration issues.

That could have been dealt at the beginning and no matter what routes that we go with, that is the first concern that I might think of, including all other contaminants or other, you know, co-active compounds that may occur or contain in the products.

I think that would be the primary concern, the interactions with other zenobiotics or other even food components, and that this can be addressed at the beginning, and if you go for the food ingredients, one aspect is, you know, possible interaction or the reaction with other food components or in chemical reactions. There's the thermal reaction. That is largely unknown territory.

So going into the food ingredient that might open the floodgate of investigating, you know, reaction product during the processing. So that consideration has to be made before we go to consider going into the food ingredients rather than dietary supplement in that case.

DR. KOWALCYK: Okay. Thank you.

Dr. Weaver?

DR. WEAVER: So I agree with the last speaker about the priority being safety of the source, the manufacturing process contaminant, but then do you need to consider different routes versus non-food having not just one?

DR. WOODCOCK: Well, the regulatory tools we have available to us in the food area only involve ingestion of a route. The drug area obviously is wide open but then you have to go through a very rigorous process to get in the drug area.

So basically many of these other routes really, you know, --

DR. WEAVER: Maybe I meant product instead of route.

DR. MUSSER: Certainly that would be, you know, in the case for cosmetics where it would be creams as opposed to food.

DR. KOWALCYK: Any other comments or questions from other Science Board members?

I think it's important for us to go ahead and look at these two questions. For example, this question is what approaches might a public agency use to manage, mitigate, or communicate potential harm? I think we've already given some scenarios there or some feedback there that (1) it's important that, you know, communicating with the public and that's really hard to do and we've seen risk communication is an area where we need a lot of development in terms of there is no AEL established yet and that we need to recognize that right now, to our knowledge, no level is safe.

And that we should probably be focusing on the -- this is what I'm hearing. I'm just reiterating -- safety of the source and, of course, one comment that struck me in I think one of the presentations, either during the Open Public Hearing, is the production and distribution of this certainly it looks

like a food supply chain.

One of the questions I had in my mind is, of course, microbial safety of these products and also there are, as Steve pointed out, Dr. Musser pointed out, there are significant differences between the way food and drugs are regulated and recognizing that producers if this were to be put into food would likely be inspected on a not a yearly basis.

DR. MUSSER: That is correct.

DR. KOWALCYK: And so I think we're averaging once every five or seven years now and when you have a product with several unknowns, in my personal opinion, that doesn't seem to be a prudent path and, of course, then how do you communicate this potential harm to the public?

I'm sure you're aware, I think one of the speakers during the Public Hearing, Open Public Hearing section showed some pictures of things that look very much like common sets that children consume and we had an incident here in Ohio where children ended up consuming a parent's -- one of their CBD or THC, I can't remember which one it was, I was trying to Google

it and my bandwidth is slow today, and ended up sick and hospitalized.

And so, you know, the idea of this getting into the pediatric population, there at least needs to be some sort of guidance around how these are marketed.

I mean, having a bag that looks almost identical to sour patch kids, you know, is asking for trouble, especially with pediatric populations that can't read. So those are just some things.

In terms of this one about what approaches might a public health agency use to manage, mitigate, or communicate potential harm, maybe we can have further discussion.

Dr. Reiss?

DR. REISS: Yes, I was just going to go down that path here just for a second.

So if I understand the presentation and my reading correctly, there's been a change sort of over time. Historically, you know, food supplements or nutritional supplements or food additives have been, you know, like for color and so on and so forth or vitamins, you know, if there was a deficiency, these

sorts of things.

Now things are moving towards this, well, there's sort of a reason. This is great to take for anxiety and so on and so forth. So we're now crossing the line of making a claim about efficacy, okay, as we talked about.

So part of the communication process can be not only saying things but maybe preventing things, I guess, too. So would it be possible, you know, from a statute perspective to sort of prevent, you know, if you can't sort of prevent these things from moving forward, can you prevent what they say about them? So just an open question if anybody wants to.

DR. WOODCOCK: Well, if you look at the shelves on the direct store, you can see that a large space is taken up by dietary supplements and their claims are not disease claims but they're more like support prostate health or support health of the GI system or what have you and over time it's grown tremendously.

Steve, isn't this like a $45 billion industry?

DR. MUSSER: Yeah. It's gone up every year. Now it's 45. It's a huge industry right now. I would mention that the CBD segment alone is four billion a year.

DR. WOODCOCK: Yeah. So they aren't allowed to make overt drug claims but dietary supplements, we don't regulate their claims, except saying they can't be drug claims and so they can support whatever support happens, something like that.

DR. REISS: Yeah.

DR. MUSSER: So from the statute perspective, that's not an option for the FDA. It would be hard for us to require that. There's a lot of First Amendment rules that would have to be dealt with there that would be extremely difficult.

DR. KOWALCYK: But if you went kind of the tobacco and alcohol route where those products do have limitations, correct, on how they can be marketed, particularly to children.

DR. WOODCOCK: That's correct.

DR. KOWALCYK: Any other comments or questions from the Science Board on this particular

question?

I'd like to go back to the previous question and just see because that question, how might a public health agency assess the unique toxicological safety questions raised by a substance outside the context of an approved drug, and I don't know as if we adequately answered that question for you and actually I want to acknowledge this is such a broad topic that there's no way to adequately answer any of these questions in a single afternoon, okay, but at least giving you some initial feedback.

I don't know if any of the Science Board members have other feedback that they'd like to provide on this. Personally, you know, I come at it from a statistician's point of view and I think that the important distinction between the food side of FDA and kind of the drug side of FDA is the null hypothesis is very different and that then makes it very difficult in terms of the evidence that you have.

So the null hypothesis in terms of drugs is that the drug is not effective until you prove that it's effective. The null hypothesis is that the drug

does not work and in the food side of things, we assume that food is safe until proven unsafe, right, and we never prove the null hypothesis and this has significant impacts on the interpretation of any data analytics that you have because the Type 1 and Type 2 errors have to be interpreted differently and so my advice to you is obviously think very long and hard about how these null hypotheses are set up.

It's actually easier to prove that the alternative that something is safe than it is to prove the alternative that it is not safe. You would need a huge number of samples to prove that something is not safe and one of my concerns in reading the background literature was that the sample sizes were quite small and you don't tend to see adverse events in that small of a population size. You need a much larger population size over a longer period of time and, of course, we've seen this even with many drugs that have gone through very thorough evaluations that years later we find that there is an adverse event that was not identified until after it started to be used by the general population.

Dr. Afshari.

DR. AFSHARI: Yes, thank you.

I agree this isn't an easy one and also I know, you know, I heard Dr. Woodcock, we're not going to speak about regulatory paths, but as I think about this aspect of it, you know, I think about weight of evidence, which again is something that we all think about and apply and then just the power of the information in the public domain and so I think as, you know, FDA was to come together alone or with collaborators as talked about earlier and start to do really systematic analyses, high-quality work around the analysis, you know, biochemical profiling, you know, and leveraging what's known from a systems biology perspective and starting to be able to put that in the public domain, you know, it's one way to start to put information out there and get some dialogues, but I think thinking about weight of evidence and knowing that potentially all the target organs or systems that could be at risk here, it's going to take a long time to solve that, but there's going to be some that are -- you're going to be able to bring some solid

data forward sooner than later.

And so I think back to the charge, you know, as you were talking there, you know, around food, just thinking again about the weight of evidence and how things go in the chemical industry and EPA and everything that NPT's done which FDA's been a partner there, it's that weight of evidence kind of falls on the side of the government to say that there's a problem here and so, you know, we know it's not an easier fast path, but I think that there are some really high-quality tools that the agency has at their disposal that could start to chip away at least at putting that high-quality kind of mechanistic information out there that could then be picked up by others who may not be able to do that work but then have additional insights and ultimately it's going to be how's that going to link to the epidemiology, you know, and that's not an easy task but those two kind of arenas are going to have to come together here, I think.

DR. MUSSER: Yeah. So I've raised my hand but I'd just like to comment briefly on that.

You're absolutely correct. I think we have in many ways opened Pandora's box here with the number of questions that we could ask for and it would go on for years and I don't think anyone really wants that. We wouldn't run out of questions and experiments for people to do.

At the same time, there's a significant number of products on the market and the agency is left with, you know, how do we communicate potential. What's the best way for us to, you know, use risk assessment or harm mitigation strategies or any other strategy to communicate our concerns to the public, to consumers, and to industry about these products, and how do we weigh in, what do we say, what's the best approach while we're at the same time trying to gather all of this data that everyone agrees we need?

DR. KOWALCYK: Thank you.

So I have a follow-up question. Are you working with CDC on looking at kind of the epidemiology of the use of this? I haven't seen much and I'm sure that's been Part 1 because this is not my focus area, but (2) because it's been illegal in many states and

areas. So it makes that kind of research challenging.

Dr. Woodcock and Dr. Musser, is there much data available on the epidemiology of chronic use of these products and are you working with CDC on that?

DR. MUSSER: So I know we do collaborate with CDC, but we can't really speak for them here. We can get you connected with them if you'd like to talk to them. There is a group, although I don't think they're doing the kind of widespread epidemiology that you would be looking for at this point.

DR. KOWALCYK: Okay. Is there anyone that's doing that?

DR. MUSSER: Patrick, do you have a name? I think you're probably more connected there.

DR. KOWALCYK: No. I mean in general.

DR. MUSSER: Oh.

DR. KOWALCYK: Is there anyone that's really looking into that kind of research?

DR. COURNOYER: Yeah. I can jump in here, Dr. Musser. There are like, for instance, in the data acceleration pilot initiatives that are described ways of obtaining just that type of information and there's

different efforts in different parts of the agency that are collaborating with external partners, as well, of various types in order to obtain data to help get a picture of that, but, you know, there are many challenges with an epidemiology approach and in particular the market is so fragmented with different types of products and different users that there's always going to be challenges, but we are working on getting epidemiological and all sorts of information about users in the real world.

DR. KOWALCYK: Okay. Thank you.

Dr. Bahinski?

DR. BAHINSKI: Yeah. Just a kind of follow-on to that question.

You know, in the drug industry there's marketing surveillance and pharmacovigilance and, you know, there are regulations around reporting adverse events when they are communicated to the sponsors.

This is my ignorance. You know, in the food industry, are there similar or, you know, with these additives guidances or regulations regarding, you know, if they receive certain adverse events notifications,

you know, communicating that it's back to the FDA, and are there ways to monitor, you know? They're not the greatest source of data, but, you know, social media sites where people may be reporting adverse reactions to some of these compounds.

DR. MUSSER: Greg, do you want to do that but largely it's voluntary. I'll let Greg explain more about -- it's not mandatory like it is with drugs but Greg can explain it more.

DR. NOONAN: Yeah. So for dietary supplements specifically, there are some mandatory from the manufacturers if they have a serious adverse event, they need to report that in. Most of the other adverse events we get are voluntary through what's called CARES. It captures both dietary supplements and other food-related but they are voluntary.

DR. KOWALCYK: But to put that into perspective, how many reports do you get annually approximately through that program?

DR. NOONAN: I am going to have to get back to you on those numbers. It's actually run through our Office of Analytics and Outreach which is a different

section. We work with them closely, but we can get you those numbers back, both general responses and we can probably even pull down some things related to cannabinoids, if needed.

DR. KOWALCYK: I understand it's substantially less than other types of systems.

DR. NOONAN: Yeah.

DR. MUSSER: It's also driven by -- you have to be careful with the numbers because it's driven by what's in the news at the time. So right now there's a lot of infant formula adverse events there, a huge spike, so, and if there's some other product that happens to be in the news, we'll see a spike in reports, but you have to look at the data carefully there and we can help strip that out for you.

DR. KOWALCYK: Well, I think my point is, is that (1) many people don't know about that system and how to report and (2) there's a lot of self-reporting bias in the system. So I just wanted to make that representation.

DR. WOODCOCK: In addition, you know, we have the over-the-counter which this is self-administration

and some people may not even necessarily connect. It's not like they've had a physician prescribe something for them. They may not connect their ingestion to whatever problem they're experiencing and then they have to go and either be seen by health care or they have to recognize.

So as I said, for some of these more dramatic events, we're seeing them from Poison Control, we're seeing them from emergency department surveillance, but we're also very worried about long-term chronic exposure which we'd be very unlikely to pick up through reporting mechanisms.

DR. COURNOYER: And I just wanted to add there, too, that self-reporting, we think it's less likely with products that are obtained, let's say, on the gray market, more marginal products. People are typically less willing to move forward with that.

DR. KOWALCYK: Okay. Any other questions or comments from the Science Board members?

DR. WOODCOCK: We will come back when we've made more progress on this. We really appreciate your input.

DR. KOWALCYK: Yes. Well, thank you, and I think it's really obvious that this topic will necessitate an in-depth engagement beyond what we can do via Zoom in one afternoon. So we are happy to form a subcommittee to study this issue further and I'd like to thank our FDA presenters and members of the public who've taken time to speak to us today.

I'd also like to again acknowledge all those who submitted written comments to the Board. We appreciate your engagement on this.

Rakesh, is there anything else that we need to do or discuss before we close? I know there's still time.

MR. RAGHUWANSHI: Just give me one moment to check in with my colleagues. Stand by, please. Thanks.

Barbara, we're good to go.

DR. KOWALCYK: Okay. Any final comments or thoughts from the rest of the Science Board before we begin the closing?

DR. SARWAL: So, Barbara, about the subcommittee that we talked about, we just follow up by

e-mail after this?

DR. KOWALCYK: Yes. Rakesh can comment a bit about that, but it sounds like we'll be forming probably three subcommittees, based on the discussions that we had today, one around the new alternative methods, one potentially around data science, seemed like there was a lot of interest in that, and then one around this specific issue.

So, Rakesh, correct me if I'm wrong, if members are interested in a particular subcommittee, they should reach out to you and I, correct?

MR. RAGHUWANSHI: Yes, that's correct, Barb. Thank you. We'll send out an e-mail to the Science Board members after this meeting as we work to establish those subcommittees for further studying those issues. There's a process that needs to be followed which includes very strict conflict of interest screening, as everybody knows, and so we'll go through the process and get that going.

DR. KOWALCYK: Dr. Ryu?

DR. RYU: Thank you.

I just wanted to praise all the effort, the

important work FDA has been doing. The sheer number of applications for the new ingredients has tripled in comparison with the past four years versus past 10 years. I bet you didn't get triple the number of staff support. So I deeply appreciate handling all those pressured requests and the workload and I will be happy to be a part to help in any way. So again, you know, thank you very much for all your work for the public.

DR. KOWALCYK: Thank you.

Any other comments, last comments before?

DR. MUSSER: Just my deep thanks for hanging in there all day. I know this was a good meeting. I really enjoyed the morning, as well, but I really appreciate your help here. This is really very valuable for us and can't thank you enough for the time spent here today.

Final Thoughts and Closing Comments

DR. KOWALCYK: Well, thank you.

So hearing no other or seeing no other hands raised, I think we can start to wrap up and just some final thoughts on my end.

I agree with Dr. Ryu. You know, the amount

of work that you have with the agency is quite impressive. I try to think about how you're going to manage dealing with these three issues on top of implementing the Food Safety Modernization Act and all the drug responsibilities that you have as well as just the ongoing issues around baby formulas, it's amazing, and I think, you know, I thank you for bringing these important topics to us. It's really nice, at least from my perspective as a scientist, to be able to provide input and this is really where the translational work is and it's a piece that I love is translating science into policy and practice.

So thank you very much for everyone's engagement today and attendance and, of course, we look forward to continuing to work with the agency to advance your public health mission and, of course, protect the health of all Americans.

So thank you very much and I think with that we can adjourn. Have a great day.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)