U.S. FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR TOBACCO PRODUCTS

+ + + + +

PREMARKET APPLICATIONS: OPPORTUNITIES FOR STAKEHOLDER ENGAGEMENT

+ + + + +

PUBLIC MEETING

+ + + + +

TUESDAY
OCTOBER 24, 2023

+ + + + +

The Meeting met via hybrid meeting, in-person at the FDA White Oaks Campus and virtually via Videoconference, at 9:00 a.m. EDT, Commander Avena Russell, MS, presiding.

This transcript has not been edited or corrected but appears as received from the commercial transcribing service.

PRESENT

CDR. AVENA RUSSELL, MS
APOSTOLOS ALEXANDRIDIS, Ph.D., MPH
BRIDGET AMBROSE
BENJAMIN APELBERG, Ph.D.
SEQUOIA BACON, MPH
ROSANNA BELTRE
CHAD BROCKER
CHRISSIE CAI, MS
TODD CECIL, Ph.D.
KAREN COYNE
ERIC CRUZ, BS
STEPHANIE DANIELS, Ph.D.
HUDA DAWOOD, BS
MAMATA DE, Ph.D.
LAUREN DeBERRY, MPH

MATTHEW FARRELLY, Ph.D.
SHANNON HANNA
LYNN HULL
MARYBETH IRWIN, Ph.D.
BRIAN KING, Ph.D., MS
RACHEL LEREBOURS, Ph.D.
MOLLIE MILLER, Ph.D.
MICHAEL MORSCHAUSER
COLLEEN ROGERS
HANS ROSENFELDT
SELENA RUSSELL
MEGAN SCHROEDER
DEBORAH SHOLTES, MS
CRISTI STARK
YUAN TIAN
LUIS VALERIO
KRIS VANAMBURG
FRAN WEISS, BS
JOHNNY WEN
SHERYL WOOD, MPH
KRISTIN WURCEL, Ph.D.

CONTENTS

P-R-O-C-E-E-D-I-N-G-S

(8:31 a.m.)

DR. FARRELLY: Okay. Well, good morning. Welcome to day two. Welcome back. Thanks for your participation and your questions yesterday. We've got another big day planned for today, including a question-and-answer session at the end.

So I'm Matthew Farrelly. I'm the new Director of the Office of Science. I've been in this role for about seven months. So I have a Ph.D. in economics, and you might wonder what is an economist doing in this role. My wife asks me that every once in a while. But my dissertation was actually looking at the role of workplace smoking policies and cigarette excise taxes on adult smoking behavior, and that was in the mid-90s, so before it was cool to be in tobacco research. So -- and ever since then, my research has focused on just that: looking at smoking behaviors, later vaping behaviors, among adolescents, young adults, and adults.

I've spent my career, even though I'm an economist, I've spent my career doing interdisciplinary work with psychologists,

sociologists, public health researchers, survey methodologists, statisticians; and I've found a lot of, you know, gotten a lot of insight by working with other disciplines. But I guess, at my core, after all of this time doing this type of work, I consider myself a public health researcher. And, in fact, I'm so committed to interdisciplinary work that I married an epidemiologist 25 years ago. And early on in our relationship, when she was having trouble sleeping, she would say talk to me about economics. And you probably already know, but economics is a very effective sleep aid, even though it's not endorsed by FDA.

And I think at the core of what I bring to the Office of Science is the idea of scientific evidence driving decision-making. In my role prior to coming to FDA, I worked at RTI International. That's an independent not-for-profit research organization. And the work that I did there was focused on doing independent evaluations of various tobacco interventions. So it's an independent organization that we didn't take sides, we weren't known to be politically-affiliated in any way. So my job was to

just look at the facts and decide what types of policies or interventions worked or did not.

And I was at RTI for over 26 years, and I did independent evaluations of tobacco-control programs and interventions at the national level and the state level. I worked with many health departments across the country, worked with the Office on Smoking and Health starting in the mid-90s, along with NCI. And then, soon after FDA's Center for Tobacco Products was formed in 2009, I started working with them in 2010 when the Center had a size of about 25 people, and I worked with them continuously through 2023 in March when I transitioned to this role at CTP.

And despite working with the Office of Science and others at CTP for so many years, I really didn't know a lot about sort of the inner workings of the Office of Science, and I was really impressed when I joined CTP to learn about the complex and rigorous application and review process, the tremendous amount of work that OS has completed, especially in recent years, and the breadth and depth of the expertise across so many disciplines in the office. Some of that was on display yesterday, and you'll see more of

it today. And the fact that they're able to take action on 26 million applications over the past few years was quite a Herculean effort, and I know there's more that needs to happen. And I credit that expertise in the office for helping me get up to speed so quickly in these past seven months.

In terms of my vision for the office, it's increased engagement with stakeholders and increased transparency in our approach to product reviews. We're looking for opportunities to increase efficiencies and streamline the internal product review process.

To address that question that Cristi so gracefully pitched my way yesterday, we are working on increasing staffing. One of the things that I did need to know about the Office of Science on day one was about hiring and staffing. I've been a manager of staff for over 20 years, so one of the first things I did was to talk with many of the hiring managers in the office to understand what their needs were, any barriers that they were encountering, and I quickly started working with our staff that focus on hiring and retention to see what I could do to speed things

along. And I'm still committed to doing that, and our goal is to increase our staff.

Another goal is to revisit our strategic research priorities and continue to conduct sound scientific reviews of product applications with a goal of improving public health. In the case of premarket tobacco product applications, or PMTAs, we aim to do this by authorizing tobacco products which have been demonstrated to be appropriate for the protection of public health. And we do that, as you know, through a really holistic view of the applications.

Another thing that you're all aware of was the Reagan-Udall Foundation review, and that brings up a number of opportunities and challenges. And despite numerous challenges posed by the application review, including managing the volume of reviews, weighing complex and evolving scientific evidence, and responding to legal decisions, CTP has made significant progress in reviewing premarket applications and is continually seeking opportunities to enhance efficiency. As Dr. King yesterday said, we are committed to operationalizing the Reagan-Udall's recommendations to strengthen the regulatory process

and operations. We see these recommendations as opportunities to improve efficiency, effectiveness, and transparency in our scientific review process, and that's why we are all excited to have this two-day meeting to kick off that process.

To this end, we are developing a more efficient framework for high-quality tobacco product applications, increasing internal communication to improve scientific engagement and deliberation. Dedicating additional resources to enhance program management and implementation and improving communication with stakeholders on scientific issues and practices. And that's what I've been doing for the past seven months is really engaging with all the different disciplines to really understand the challenges and opportunities to improve the product review process and also to communicate that to applicants.

So this workshop is an opportunity to have an open dialogue with you about some of your lessons learned and program and process improvements. It's also an opportunity for us to hear from you and your questions, like we did yesterday, and any challenges

you have. And to that end, I look forward to our Session 7 Q&A at the end. We've received over a hundred questions already, which we've been looking at and preparing answers for. And we have a full agenda today of scientific presentations. And I want to welcome everybody once again, those of you who have joined online, and I'll turn it over to our facilitator to get us kicked off.

So, once again, thank you for being here. We really appreciate it. And I look forward to meeting you later.

(Applause.)

CDR. RUSSELL: Thank you, Dr. Farrelly, and thank you for the warm welcome and opening remarks.

Good morning. It's day two, and I am Commander Avena Russell. I'm a United States Public Health Service commissioned officer. I am a branch chief within the Division of Regulatory Project Management, and I will be your moderator again today. We're on the second day, you guys, so we're just trucking right along. Can you hear? Thank you.

I have a few logistics for today. As

similar to yesterday, we will go over the logistics, recap the overview of the meeting, and include some of our expectations. For today, we will break once before lunch. We anticipate breaking for lunch on or about noon. Lunch options are available within the lobby at the kiosk. All lunch items must be purchased before 10 a.m. in efforts to have your lunch here on time.

This meeting is being recorded. A transcript for each day will be posted on CTP's website after the meeting.

For the last of the logistics, as noted yesterday, as part of our registration process, we provide an opportunity to submit questions in advance, and many of you did so. If you have suggestions on premarket review topics for future regulations and guidance or any topics not covered within the scope of this meeting, you may send your suggestions to CTP regulations at fda.hhs.gov. The email address is posted outside on the registration table.

A panel session will follow each group of presentations. Questions or clarifications will not be taken during the presentation time. Like

yesterday, we are asking and we will be taking live questions from our in-person and virtual audience for each panel session. The questions taken during a live session will be for that topic only. We will revisit other topics during Panel 7 where we will have an open question-and-answer period.

We encourage our face-to-face audience, as well as our virtual audience, to provide any questions. Virtual audience, you can submit them via the chat function. Our face-to-face audience, you can utilize the index questions, the index cards available at the registration table, or there will be some FDA staff providing them throughout the room within the meeting.

Please be sure you clearly communicate what you intend to ask and write neatly. We are also asking that you please identify yourself and your organization on your index card. If your questions do not get answered during the panel discussion or you have additional questions, you can submit those to askctp@fda.hhs.gov.

As a reminder, FDA does not intend to address or discuss anything outside of the scope of

this meeting. This includes any pending applications or litigation, future rulemaking, potential enforcement discretion policies, or any new policy not previously communicated in guidance or rulemaking.

We'll now begin with Session 1 -- I'm sorry, Session 4 of Day 2, FDA Review - Product Characterization. The first presentation will discuss best practices for submitting complete ingredient and HPC information in PMTAs by Dr. Stephanie Daniels, followed by Rachel Lerebours and -- excuse me -- Dr. Rachel Lerebours and Dr. Kristin Wurcel discussing leachables and extractables.

Dr. Daniels.

DR. DANIELS: Good morning. My name is Stephanie Daniels, and I am a chemist in the Division of Product Science within the Office of Science. The title of my presentation today is Best Practices for Submitting Complete Ingredients and HPHC Information in the Premarket Tobacco Product Applications. This presentation is intended to assist those seeking marketing authorization for a new tobacco product under the PMTA review pathway. This presentation will cover common issues CTP frequently finds in PMTA

submissions, and we'll also discuss how applicants can address these issues from a chemistry perspective.

The agenda for this presentation will focus on the following topics: ingredient information, harmful and potentially harmful constituent evaluation, product stability, comparative data, and tobacco product master file.

A common issue that has been observed with PMTA submission has been insufficient ingredient information. Applications have been missing functions of each ingredient. For example, the applicant fails to include ingredient if the ingredients are flavors, humectant, processing aids, or solvents. The chemical abstract service number and FDA unique ingredient identifier for each ingredient has also been missing in some of the applications. Some applicants have also failed to include the single ingredient information comprising the complex ingredients. For example, the new products may contain 15.3 milligrams per gram of the complex flavor rainbow gelatin. However, the applicants fail to include the individual ingredients comprising the complex ingredient.

We have also received PMTA submissions

where the applicant has failed to list the ingredient quantity in mass per unit for each ingredient. For example, ingredients are often reported in percentages weights without identifying the denominator or specifying the original unit of the numerator and the denominator. For example, the rainbow gelatin flavor contains 30 percent -- I'm sorry. The ingredients for the complex ingredient was reported in percentages.

Some applicants have also failed to include the full details on the nicotine source. For example, the new product contains nicotine. However, the applicant did not state whether the nicotine is derived from tobacco or if the tobacco is synthetic. Information on the nicotine source has been helpful in making a determination that marketing of the product would be appropriate for the protection of public health.

Requirements for ingredient information. Per the PMTA final rule, the applicant is required to provide the function of all ingredients. For example, the applicant must list whether each ingredient is a flavor, humectant, processing aid, or a solvent. The applicant must also include the CAS number or UNII if

available.

Submissions should report all ingredient quantities as mass per unit of use for a portion product or a mass per gram of a product for a non-portion product. For example, milligram per cigarette or milligram per pouch or milligram per gram of product.

Okay. If the new product contains a complex ingredient, the applicant is required to provide the name, CAS number, function, and quantity of the individual ingredients that make up the complex ingredients. The applicant is also required to report the quantities of each chemical compound in the complex ingredient separately.

FDA evaluates whether the sum of the individual ingredients equal the quantity of the complex ingredient. For example, if the complex ingredient rainbow gelatin contained, if the new product contains 15 milligrams per gram of the complex ingredient rainbow gelatin, the individual ingredient should sum 15 milligrams per gram.

CTP has also encountered applications with missing comparative data. Applications have been

missing HPHC data for a comparative product. Comparative HPHC data should include products within the same category and subcategory, as well as products from a different tobacco category. For example, a comparative product could be a combusted cigarette, smokeless tobacco product, and/or ENDS. Some PMTAs have failed to include adequate information on the comparative products in HPHC data. For example, the new product is an ENDS product. The applicant has provided HPHC data for combusted cigarettes. However, the applicant failed to include HPHC data for currently marketed ENDS products.

Requirements for comparative HPHC data. Comparative HPHC data between two tobacco products is critical in determining the health effects of product switching. Per the PMTA final rule, the applicant is required to provide comparative HPHC data for products within the same category and subcategory, as well as products in different categories. For example, if the new ENDS product is marketed as a replacement for combusted cigarettes, consider using cigarettes and similar ENDS products as the comparison product.

In the case of ENDS product as the

comparative product, the applicant should include the ENDS name and brand, the nicotine type/form and nicotine concentration, as well as the PG/VG ratio, the flavor, and other ingredients in the comparative products. It is helpful for FDA to understand the applicant's rationale and justification for comparative products chosen, whether within the same category or a different category of the tobacco products.

The applicant must also include testing of HPHCs and parameters that may be generated from the ingredients in the tobacco products and that are known constituents of that tobacco type. The applicant must also provide a description of why the HPHCs that were tested are appropriate for that type of product.

Chemistry recommendations for comparative data. CTP has found it helpful to generate HPHCs of the new products and the comparison product in similar conditions. For example, the applicant should use comparable units, use both intense and non-intense smoking regiments to generate HPHC data for the new and comparison products, and use identical puffing regimens.

FDA has published a draft guidance for industry on reporting harmful and potentially harmful constituents in tobacco products and tobacco smoke for cigarettes, and this guidance is currently under -- currently available for comments. Here is the abbreviated recommended HPHCs for cigarettes.

When using ENDS products, an applicant would not be required to perform testing for all HPHCs. Rather, the applicant would be required to perform tests for constituents that are contained within and can be delivered by the type of product. The applicant should provide a description of why the HPHCs that were tested are appropriate for that type of product.

FDA has published a guidance titled Premarket Tobacco Product Application for Electronic Nicotine Delivery Systems, which is currently available for comments. And listed here are the recommended HPHCs for the ENDS product.

In addition to the constituents, FDA recommends that the pH of the e-liquids be tested and the resulting aerosols reported. FDA may request additional HPHCs based on the ingredients of the

tobacco product.

Incomplete HPHC testing and evaluation of the new product has also been an issue with PMTA submissions. Applications have been missing complete HPHC data for the new tobacco product. For example, the applicant may provide HPHC data generated using only one standard smoking regimen which does not include the various smoking intensities of the consumers. Another example is the application only contains partial HPHC data.

Additionally, applications have been missing analytical testing methods and protocols used to generate HPHCs. For example, the applicant only provided limited details on the testing methods used to generate the HPHCs. We have also seen applications where the applicant failed to include the validation reports for the methods described in the application.

Requirements for testing methods used for HPHC analysis. HPHC information helps FDA assess potential health risks which must be considered as part of the determination for whether permitting the marketing of a new product would be appropriate for the protection of public health. As stated in the

PMTA final rule, the applicant must provide a complete HPHC data set for the new tobacco products. FDA expects that the applicant will provide HPHCs as appropriate for the new product. For example, if the new product contains glycerol, consider testing for diethylene glycol.

In addition, validation of all analytical testing methods is required to be included with the PMTA submission. This information is needed to ensure that the methods are reliable and suitable for the intended purpose. Validation parameters include but are not limited to accuracy, precision, limit of detection, and limit of quantification.

The applicant is also required to provide full details on the test methods used to generate the HPHC data for the new product, as well as the comparative products. The application must include a complete data set for all tobacco products, such as reference product data set, number of replicates tested, standard deviation, and a summary of the results for all testing performed.

The applicant must also provide a complete description of the test protocols and methods used

which would include information on the testing laboratory and their accreditation, method validation status, validation report and data for each testing method, the length of time between date of manufacture and date of testing, as well as the storage condition prior to initiating testing.

Recommendations for testing methods used for HPHC analysis. CTP has found it helpful when applicants provide HPHC data using smoking regimens to reflect a wide-range of smoking intensity. For example, HPHC data for the tobacco product should reflect testing using both intense and non-intense smoking regimens. When using standard methods, if there are any deviations of those methods, an explanation should be provided in the PMTA submission. By providing both an intense and non-intense smoking or aerosol generating method or regimen, FDA will have a better understanding of quantities of each constituent that may be produced by the tobacco product when used under different conditions. In the past, FDA has considered a 95-percent confidence interval to be scientifically valid.

FDA has published a draft guidance titled

Validation and Verification of Analytical Testing Methods used for Tobacco Products that discuss in detail method validation. This draft guidance is currently available for public comment.

Product stability information is needed to establish the shelf life of a new product. Here, I describe four parameters: shelf life, chemical stability, extractables, and leachables, that are key to understanding the product stability. The shelf life of a product is the length of time a product is determined to be stable under normal conditions. Chemical stability determines HPHC levels are not changing significantly over time at the same property and characteristics that it possessed at the time of manufacturing. Extractables are organic and inorganic compounds that can be released from components of the container closure under worst-case scenario, and leachables are organic and inorganic compounds that may be released from the component of the container closure under normal conditions. In this presentation, I will focus on shelf life and chemical stability as extractables and leachables will be presented in detail by my colleagues immediately

following this presentation.

Lack of product stability data. Applications have been missing information on the shelf life of the new product. For example, the applicant states that the new product has a shelf life of 12 months. However, the applicant fails to provide a description of how the shelf life is determined.

PMTA submissions with incomplete chemical stability data has also been an issue. For example, the application lacks data on relevant chemical parameters of the finished product under standard storage conditions, as well as the application lacks stability testing on the container closure system. Some applications have also been missing stability testing methods and validation reports.

Requirements for product stability and shelf life. As stated in the PMTA final rule, the applicant is required to provide the length of the shelf life of the new product. For example, if the new product shelf life has been established to be 12 months, the applicant is required to provide long-term chemical stability data for the beginning -- I'm sorry. Yes, for the beginning, middle, and end time

points. PMTAs for cigarettes and roll-your-own tobacco products do not need to provide the shelf life and stability information.

Per the PMTA final rule, the applicant is also required to evaluate HPHCs and parameters to determine product stability under normal storage condition. CTP suggests testing the pH, nicotine, aldehydes, and diketones.

The applicant is also required to provide full details of the testing methods for the stability testing used. For example, at a minimum, the applicant is required to provide a complete validation report for each method to show the method is suitable, provide storage conditions prior to testing, provide product manufacture and testing dates, as well as complete information on the testing laboratory.

In some cases, applicants may rely on TPMF to fill in information for the new product that is not included in the applicant's PMTA submission. TPMFs are used to permit a person that owns the TPMF to authorize other persons to rely on information in the TPMF to support a submission to FDA without the TPMF owner having to disclose the information to the other

person. These files typically contain trade secrets and/or confidential commercial information that the TPMF owner does not wish to make public.

Issues and requirements for TPMFs. The issue CTP has encountered is, in some cases, the applicant has relied on the TPMF, but the information the applicant is referring in the TPMF cannot be found in the TPMF content or in its amendments. For example, the complex flavor rainbow gelatin was cross-referenced in the PMTA submission. However, the content for the rainbow gelatin is not found in the TPMF.

The applicant is required to ensure that the reference information, for example complex ingredients, product characterization, manufacturing and process data, or research findings, is included in the TPMF being referenced. It is a responsibility of the PMTA applicant to ensure that all data and information is provided in their application. In the case where a TPMF is referenced in a PMTA, it is recommended that the applicant of the PMTA verifies with the TPMF owner that the reference information is included in the TPMF that is being cross-referenced.

If there are any questions on the content of the referenced TPMF, the PMTA applicant should contact the TPMF owner.

In summary, this presentation has covered most common issues encountered by CTP when reviewing new tobacco products via the PMTA pathway from a chemistry perspective. These issues include insufficient ingredient information, incomplete HPHC evaluation, missing product stability data, inadequate comparative data, and deficient TPMFs.

When submitting a new tobacco product via the PMTA review pathway, per the PMTA final rule, the application must include a complete list of all ingredients, all relevant HPHC data and testing methods, chemical stability data over the shelf life of the new product and detailed analytical testing methods, the shelf life of the new product and a description of how the shelf life is determined, as well as comparative HPHC data of the product within the same category and subcategory and products in different categories.

If there are any questions related to this presentation, please ask on the panel discussion or

submit questions to askctp@fda.hhs.gov. And with that, I would like to thank you for your time.

(Applause.)

DR. LEREBOURS: Good morning. My name is Rachel Lerebours. I'm a chemist in the Division of Product Science in the Office of Science. Today, my colleague, Kristin Wurcel, a toxicologist from the Division of Non-Clinical Science, and I will be presenting on extractable and leachable studies.

Before I begin the presentation, I want to relate one of our learnings from reviewing electronic nicotine delivery systems, or ENDS, premarket tobacco applications, or PMTAs. Specifically, we have seen a lot of ways applicants have assessed leachable constituents in their products. Many of the applications are lacking the information that we need to complete our assessments in chemistry, which leaves our colleagues in toxicology with fewer concrete facts to consider when evaluating the overall toxicological risk of a product. In our guidance on PMTA for ENDS and in the 2021 PMTA rule, we have indicated that the extractable and leachable information is recommended and required respectively. We would like to take this

opportunity to offer a summary of extractables and leachables in the context of tobacco product review.

So today our objective is to explain extractables and leachables in the context of tobacco product review and provide an overview of the type of information that can be provided. We will briefly define extractables and leachables, describe the relationship between them, stress their importance based upon literature, national, and international standards. We will also list a few common leachables of concern that we have found in applications we have assessed. We will then discuss the information that you may wish to include in ENDS PMTAs with respect to extractables and leachables.

So why are we concerned with leachables in products? Leachables are impurities that can affect the product in various ways. Leachables can interact with the products, potentially altering their characteristic stability and shelf life. In addition, leachables can be toxic and ENDS users can be exposed to them.

In the next few slides, I'd like to define a few terms we'll use for the purpose of this

presentation. The part of the product that is burned, aerosolized, inhaled, ingested, or absorbed during tobacco product use will be called the consumable part. Examples include, but are not limited to, e-liquids, smokeless tobacco, cigar filler, cigar binder, and cigar wrapper. Any component either in contact with the consumable part during storage or determined to be of particular interest to include an extractable or leachable study will be called a critical component. Examples include, but are not limited to, an atomizer holding an e-liquid, bottle and cap on an e-liquid bottle refill, coils, and can for loose or apportioned tobacco.

While I have just described these expressions in terms of many different types of tobacco products, for this talk, we will focus on E&L evaluations of ENDS products.

A container closure system as defined in the 2021 PMTA rule is a subset of packaging also defined in the rule. For example, the carton holding multiple e-liquid bottles is considered part of the overall packaging and each bottle holding the e-liquid is considered the container closure system. Packaging

that constitutes the container closure system is intended or reasonably expected to affect or alter the performance, composition constituents, or characteristic of the tobacco product, such as leaching substances that are then incorporated into the consumable tobacco product.

Packaging that is not the container closure system is not intended, nor reasonably expected, to affect or alter the performance, composition, constituents, or characteristic of the tobacco product and is, therefore, not a component or part of the tobacco product. Thus, the CCS includes some, but not all, critical components. The reason we make this distinction is because for certain products, such as cartridges, the CCS does not encompass all critical components. For example, the CCS does not include wicks and coils. However, wicks and coils are likely to produce leachables, as they are in direct contact with the e-liquid during storage, thus should be included in the critical components.

So here's the meat. What are extractables and leachables? An extractable study measures what can migrate from the critical components of a

container to the product. A leachable study measures what does migrate from the critical components of a container to the consumable part of the product under use or storage conditions. Thus, extractables are constituents released from the critical components of a container into the consumable part of a product during laboratory conditions. It means it mimics a worst case scenario.

Leachables, on the other hand, are constituents that transfer from the critical components of a container into the consumable part of a product under normal conditions. It means it mimics a more realistic scenario.

So the extractable study and the leachable study are two individual, yet related, studies. The design of the leachable study is informed by the outcome of the extractable study. Extractable studies, by testing the material under aggressive conditions, show possible constituents that may enter the product. Thus, extractable studies help predict what type of constituents will likely be observed in the leachable study. These two studies facilitate understanding of the overall characterization and

stability of product.

The difference between an extractable study and a leachable study is that an extractable study tests the material, such as what constituents come out of a plastic bottle, while a leachable study tests the product, such as what unexpected constituents come out of an e-liquid.

At this time, I'll give the floor to my colleague, Kristin Wurcel, to discuss the toxicological aspects of E&L.

DR. WURCEL: Thank you, Rachel. Good morning. My name is Kristin Wurcel, and I am a toxicology team supervisor. Today, I will be discussing some considerations regarding extractables and leachables from the toxicology perspective.

ENDS aerosols are complex mixtures that contain several constituents that might include constituents identified as harmful and potentially harmful constituents known as HPHCs, thermal degradation products, and other reaction products, ingredients, and leachables. Therefore, users of ENDS will be exposed to leachable compounds. To help understand the health risks of a tobacco product, FDA

recommends, among other things, providing a full assessment of the toxicological profile associated with the ENDS under review.

Leachables may be present in ENDS aerosol. Leachables, along with other aerosol constituents, can contribute to the overall toxicological risk of ENDS and should be considered as part of this risk assessment. Unless there are data to the contrary, the most conservative approach in a toxicological assessment is to assume that leachables identified in ENDS e-liquids will transfer completely to the aerosol. However, if data indicate that leachables identified in e-liquid do not transfer to the aerosol, then those leachables that do not transfer to aerosol would not be of toxicological concern because they would not result in exposure to users of the product.

Many example leachables have been reported in ENDS PMTA and the literature. The table at the bottom of this slide includes example leachables that we have seen from these data sources. Several of these leachables are on the HPHC list, including arsenic, cadmium, chromium, lead, nickel, and selenium, which are bold red text on the slide. These

HPHCs have well-recognized adverse health outcomes for both cancer and non-cancer effects.

On the other hand, many of these leachables are not established HPHCs. However, although these leachables are not established HPHCs, they may have associated toxicological risks. For example, bisphenol A is associated with adverse health effects on the immune system, and phthalates, such as diethyl phthalate, may cause adverse reproductive and developmental effects. Note: these leachables and associated toxicities are examples and are not intended as an exhaustive list of all potential leachables and their associated toxicities for users of ENDS.

Because the leachables identified in ENDS are variable, the toxicity associated with leachables in a specific ENDS will depend upon the leachables identified in that product. In the hypothetical example ENDS at the bottom of this slide, each ENDS has a distinct leachable profile. Therefore, the risk attributable to leachable compounds in each ENDS is unique.

Now that we have established the

importance of leachables in contributing to the overall risk of ENDS, I would like to discuss thresholds in extractable and leachable study design. First, I will focus on what is called the SCT or TTC. The term safety concern threshold, or SCT, is defined for established practices regarding drug products. However, since tobacco products are not safe, the term TTC, or threshold of toxicological concern, may be more appropriate.

For drug products, the SCT is a threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects. For tobacco products, leachables may be present at levels which would not contribute meaningfully to the overall toxicological risk of that tobacco product. These levels are often described as a TTC level. Below that level, toxicological evaluation of such leachable compounds are generally not needed to inform the risk of ENDS.

Additional information about the use of TTCs in PMTAs will be discussed in Session 6.

A TTC is in units of exposure. For

example, micrograms per day. However, for analytical studies, the TTC needs to be in units of concentration, such as micrograms per component or micrograms per mil, to allow for measurement. A TTC can be used to derive an analytical evaluation threshold, or AET, which is in units of concentration to allow for measurement.

In deriving the AET from the TTC, there is no single equation that would be appropriate for all ENDS. This is because there is a wide range of characteristics in ENDS, such as device or component variability in size or volume, different product use patterns including number of puffs per day, and unique methodologies that may be used to conduct extractable and leachable studies, such as whether leachables are measured in e-liquid or in aerosol. Importantly, the calculations and assumptions used to generate the AET are relevant to the reliability and applicability of the AET.

Earlier in this presentation, my colleague discussed the relationship and key differences between extractables and leachables. Because leachables may better represent user exposure conditions, the

leachables data, rather than the extractables data, may be more informative in the evaluation of the risk of ENDS. Extractable studies are important to inform the design of leachable studies. Additionally, in a real world scenario, all leachables may not be identified in an extractable study. Therefore, conducting only an extractable study may not identify all potential leachables in an ENDS to which users could be exposed.

Overall, leachables in ENDS can contribute to the toxicological risk of new products in PMTAs, along with other constituents in ENDS aerosol that may result in user exposures. Additional information about the risk evaluation of leachables and other constituents will be discussed in Session 6 of today's meeting.

At this time, I will give the floor back to my colleague, Rachel Lerebours.

DR. LEREBOURS: Thank you, Kristin. While toxicology evaluates the risk assessment associated with E&L, chemistry evaluates all aspects related to methods and validation. Specifically, chemistry evaluates the study design and reliability of the

measurements, including analytical sampling plan, analytical measuring plan, fit for purpose, and peak constituent identification. An example of an E&L study typically begins with a study design followed by the extractable experiment created from clear method development and validation plan. The data acquired from the experiment are assessed and used for the leachable method development. Once the method is validated, the leachable study is conducted and the results are evaluated in a risk assessment.

As reviewers, our primary questions are: Are methods used adequate and suitable for their intended purpose? What constituents are observed during E&L experiments and how are they identified? Are observed measurement concentrations high or low? If anything is missing from the methodology, is there an explanation with scientific justification for the omission or deviation?

Is the extractable study method adequate? For extractable method development, the major decisions to make are selections of solvent, conditions, and analysis type. The selections of solvents and conditions are critical because solvents

and conditions should be harsh enough to pull out constituents but not degrade the critical components and capture the consumable part of interest. Solvents might include organic solvents for volatile and non-volatile constituents and acids for metals. Conditions might include temperature, types of agitation, durations, and volume. The report might consider the type of analysis used and why. Extractable method analysis might be qualitative or semi-quantitative. The selection of analysis type affects the type of validation that you may want to consider. The type of validations to consider will be described later in this presentation.

Is the leachable study method adequate? For leachable method development, an initial decision is which consumable parts should be assessed. For example, in ENDS products, consider whether to assess a simulated e-liquid, as opposed to the finished e-liquid. It is important that tested e-liquids have similar physical and chemical properties and bracket the finished products or e-liquids likely to be used in the product.

Similar to extractable studies, leachable

study conditions should be carefully chosen to ensure proper conditions to appropriately capture leachables. Conditions to consider include duration of the experiments, temperature, humidity, and sampling times. Typical leachable studies are conducted under ambient temperature over the shelf life of the product. Analysis selection type might be semi-quantitative or quantitative for leachables and depend on the purpose of the leachable study. The application must include a description of method procedure, method validation information, and a rationale for selecting each test method.

Are the sampling methods appropriate? For both extractable and leachable studies, it is important to choose sampling methods that are appropriate for the type of analyte that is expected. For example, liquid-liquid extraction, or LLE, is beneficial for non-targeted analysis because it's not as selective as other techniques. Solid phase extractions, or SPE, is more appropriate for the targeted analysis because the sorbent material is selective. Solid phase microextraction, or SPME, is appropriate for the preparation for the analysis of

both volatile and non-volatile constituents. Lastly, dispersive liquid-liquid microextraction, or DLLME, is more appropriate for the preparation for the detection of low-level leachables due to the low solvent volume needed.

Is the instrumentation method appropriate? Similarly, it is important to select the appropriate instrumentation to detect the analyte being examined. Elemental impurities, metals, inorganic compounds are detected via inductively coupled plasma, or ICP, combined with mass spectrometry, or MS, or optical emission spectrometry, OES, or atomic emission spectroscopy, AES. For polycyclic aromatic hydrocarbons, or PAH, in semi-volatile compounds, they are best detected via gas chromotography, GC, combined with MS, while volatile compounds are best detected via head space GCMS.

For non-volatile compounds, best detection methods include liquid chromotography, or LC, combined with MS. Please note that this list is not exhaustive. These are examples. Other methods can be used, as well as orthogonal complementary techniques.

Are the results reliable? Different

analysis types require different validation methods. This slide shows how qualitative, semi-quantitative, and quantitative methods can be validated and what is suggested to be included with the validation report for each type. For qualitative validation reports, consider including instrument limit of detection, or instrument LOD, resolution, mass accuracy, and mass range. For semi-quantitative method validations, consider including limit of quantization, or LOQ, and selectivity. Quantitative validation reports are more robust and include LOQ, accuracy repeatability, accuracy intermediate, precision, robustness, selectivity, and linearity range.

Of all validation parameters, LOQ is especially important for E&L studies because it helps determine if the constituents can be reliably determined relative to an established AET.

Methods to identify constituents. When submitting an E&L study, it is important to identify all constituents above an established AET. The identification report may include spectral library used, methodology, confidence level for the identification, and any additional supporting

information. Additionally, the report may include the number of constituents at each confidence level and a discussion regarding why constituents at each confidence level do not raise potential toxicological concerns.

This slide explains what is meant by confidence level. When elucidating the structure of a constituent, challenges may be faced which may result in being unable to completely elucidate the structure. As such, multiple confidence levels may be cited with the resulting constituent depending on how much can be elucidated and the type of evidence available to support the structure.

For example, a confirmed Level 1 structure will typically provide an isometrically-accurate constituent name and can be accompanied by an MS and retention time match with an authentic reference standard. A confident Level 2 structure will typically provide a constituent name and can be accompanied with a library match and supporting orthogonal complementary data and information that relates it to the critical component being assessed. A tentative Level 3 structure may provide potential structure or

class and can be accompanied with a library match and an isotope adduct.

Partial and unidentified structures, Level 4 and 5 respectively, are usually considered low confidence, providing minimal structure information. It would be helpful to provide a discussion of confidence level and identity of any constituents above an AET that you have set in your application for E&L studies.

While it is preferred that E&L study appears in the module three or module four of the PMTA, other locations are acceptable, as long as it's clearly labeled in the table of contents, TOC. Alternatively, E&L studies can also be included in tobacco product master files, or TPMF. If E&L information is located in the TPMF, the main application documents should clearly mention the TPMF submission tracking number, or STN, and also include a letter of authorization, LOA.

So today we have described the importance of E&L in contributing to the overall toxicological risk of ENDS products, the E&L evaluation process, and provided the information we look for, which includes

adequate study information with supporting rationale. It is important to provide scientific justification for all decisions, protocol deviations, and unexpected results.

Some examples of decisions can be which critical components to test and which e-liquids to use for a leachable study. Some unexpected findings can be more leachables than extractable products in many unidentified or partially identified constituents. These are only examples. There may be other unexpected scenarios. It is important to provide an explanation of why unexpected scenarios do not raise concerns.

Lastly, as a reminder, there's a presentation discussing risk evaluation of leachables and other constituents in Session 6.

Some parting gifts. This slide includes full citations of rule, guidance, and non-tobacco standards that may be useful. The next two slides list non-tobacco literature that may be useful in designing and analyzing E&L studies. And then, lastly, this slide shows method abbreviations used on some slides -- oops, not this one. This one. Method

abbreviations that were used on some slides are defined here.

If you have any questions, please don't hesitate to ask at our panel discussions. And we hope you have found this information helpful in your efforts to develop applications. Thank you so much for your time.

(Applause.)

CDR. RUSSELL: Well, someone is ringing. Thank you, guys, for that great information. Thank you to our presenters. We will now move to the panel session for this presentation.

While they are getting situated, I will give some brief bios of the panelists. Our panelists for today are Dr. Stephanie Daniels. Dr. Daniels is a chemist in the Division of Product Science in the Office of Science. Dr. Daniels joined CTP as a chemistry reviewer scientist in 2017. In addition to tobacco product reviewer, Dr. Daniels is active in research and development of smoking regimens for generating and quantitating HPHCs for smoking pipe tobacco.

Before joining CTP, Dr. Daniels completed

a postdoctoral fellowship at Oakridge Institute for Science and Education supporting FDA's Center for Drug Evaluation and Research. Dr. Daniels holds a PhD in analytical chemistry from Louisiana State University and a master's and bachelor's in chemistry from Jackson State University. Welcome back, Dr. Daniels.

Dr. Selena Russell. Dr. Selena Russell is a senior chemist in the Division of Product Science in the Office of Science. Dr. Russell joined CTP as a chemistry review scientist in 2017. Her work includes tobacco product application review. Before joining CTP, Dr. Russell was a postdoctoral fellow at the U.S. Army Research Laboratory where she developed new electrolytes and battery chemistries to improve battery safety and performance with a focus on electrode-electrolyte interfaces and interphases. Dr. Russell received her PhD in physical chemistry from Iowa State University where she studied mass transport of surfaces. Welcome, Dr. Russell.

Dr. Kristin Wurcel. Dr. Wurcel is a supervisory pharmacologist in the Division of Non-Clinical Science in the Office of Science. Dr. Wurcel joined CTP in 2018 as a toxicological review scientist

and became a toxicology team supervisor in 2021. Dr. Wurcel currently supervises a team of toxicology reviewers who are active in tobacco product application review, other regulatory science assignments, and research projects. She also provides scientific training on toxicology and risk assessment topics to her division.

Before joining CTP, Dr. Wurcel was a researcher in academia in military settings where she studied the pharmacology of the tobacco constituent nicotine in the context of nicotinic receptor structure and function in traumatic brain injury. Welcome, Dr. Wurcel.

Last but not least, Dr. Todd Cecil. Dr. Cecil is the deputy director of Regulatory Management in the Office of Science. Dr. Cecil joined CTP as a chemistry review scientist in 2015 and progressed to managerial positions until he served as the associate director of the Division of Product Science. In his position, he oversaw the evaluation of the composition and design of tobacco products. In addition, he served on the leadership team where he was involved in chemical, microbiological, and engineering research on

tobacco products resulting in numerous publications in peer reviewed journals.

In 2020, Dr. Cecil became the deputy director of CTP's Office of Science where the leadership team in the office share responsibility for reviewing tobacco product applications. Dr. Cecil's particular focus is on substantial equivalence reports and exemptions from substantial equivalence requests.

In addition, Dr. Cecil participates in aspects of premarket tobacco application product review, provides scientific support for regulations and guidance, evaluates the knowledge base for regulatory decisions, and carries out research to fulfill the gaps in scientific knowledge related to tobacco product regulation.

Before his tenure at CTP, Dr. Cecil worked for over 20 years at the United States Pharmacopeia Convention, USP, including ten years as the vice president of Standards Development. USP is a non-profit standard-setting organization for the pharmaceutical industry. In his role, Dr. Cecil authored and contributed to hundreds of pharmaceutical standards and chapters with broad industry impact,

including a revised standard for metal impurities in pharmaceuticals. In his role, he traveled extensively and presented at hundreds of national and international symposia and training sessions throughout the world. Welcome, Dr. Cecil.

Let's get started with our first question. Do we have any questions from the audience? We will do a two-to-two ratio as we did yesterday. If you have any questions, please feel free to come up to the microphone in the middle and ask your question.

MS. ZDINAK: Hi. Good morning. Jessica Zdinak from ARAC. My question is how did you determine when you put up, the previous presenter put up the two slides that had the references that said these are non-tobacco related references that we may find useful. What are the steps that you guys take when you're looking to identify non-tobacco based research to help guide assessments within, you know, our studies for the applications? Are there specific, like, requirements or things that you guys check off to make sure it's relevant? Because sometimes when we see the assessment of a non-tobacco related field to tobacco related, it's kind of difficult to draw that

parallel. So why were those selected and what steps do you guys take to make sure they're relevant? Thank you.

DR. RUSSELL: Thank you for your question. So there's not a ton of literature for the tobacco product extractables and leachables, so we look at the non-tobacco field and any of these other extractable and leachable studies that are out there to help gain more knowledge about how these studies are run, what are good practices, and these types of things, and then extrapolate those out. So papers that are well respected, well referenced, and these types of things are helpful in informing kind of our thoughts and what type of information could be provided and gleaned from these type of studies.

DR. CECIL: It's also important to look at national and international standards that were developed for products of a similar type. They may not be tobacco products, but they are orally-inhaled products. The standards from the USP and from ISO are for inhaled, dry powder inhaled and for liquid inhaled or inhalers in the pharmaceutical industry, so it's a similar application. And it is also a liquid that has

the potential to extract and have leachables come from the rubber or the other source of the CCS closures.

So there's a lot of similarity between those types of products. So, therefore, the applicability is the most obvious.

CDR. RUSSELL: Thank you for your question. Do we have any other additional questions from the audience? I do have a question from the virtual audience. Are there any laboratories recognized by FDA in order to conduct the necessary requested testing for the ingredients and to submit the analysis?

DR. CECIL: FDA does not test laboratories. It's up to the manufacturer to determine whether or not an individual laboratory has the capability to do the testing that you need to do, and that would be part of your contracting with that individual company. There's some very good companies out there that are very capable, and so we can't point to any, but we have confidence that you'll find the right folks and provide the data that we need so that we can determine that it was done the right way.

CDR. RUSSELL: Do we have any other

questions from the audience? We do have another question from the virtual audience. What is the recommended sample number for HPHCs?

DR. DANIELS: We don't have a requirement for the number of samples to be tested for HPHCs. However, typically, what we've seen has been five to seven replicates for HPHCs.

CDR. RUSSELL: We do have another question from the face-to-face audience. Can you please explain what you mean by orthogonal studies and where we would need to use those types of studies?

DR. RUSSELL: Thank you for the question. So orthogonal studies would be other types of analytical measurement techniques that you could use to confirm an identification. So perhaps your initial technique is a mass spectrometry, so you could use, you know, again, a high-resolution mass spectrometry, an NMR, or an optical method, or just different kinds of analytical methods to help confirm your identification of the compound. This is especially helpful in confirming functional groups and backbone structure and these kinds of things, so orthogonal is just additional analytical methods.

CDR. RUSSELL: Do we have any additional questions from the audience? I think we have one question coming down. We've got a few from the virtual audience.

Can one of the panelists say more about the source of nicotine being relevant to a determination of whether a product is a PPH? For example, is a product made by synthetic nicotine more likely to be determined to be a PPH than one made with tobacco-derived nicotine?

DR. CECIL: I was voted off the island. I can answer this one. When we look at synthetic nicotine versus natural-sourced nicotine, nicotine is largely nicotine except for the fact that we've got an R and an S form of nicotine. When we are looking at these materials, there's a lot of data on one form, one chiral form of nicotine, and the other is a little less well known. There are interactions reported in literature that suggest that there may be concerns with, I believe it's the S form -- or R form, did I get it wrong? Hence, my stalling there. But in any case, looking at the R form, there are interactions with pharmaceuticals and other potential concerns that

have not been well developed, and so we would have greater concerns about a 50/50 racemate of R&S versus a R-to-S ratio that is similar to a natural source, which is greater than 95 percent of the S form.

CDR. RUSSELL: Thank you. We have a virtual question. Is the mouthpiece of a device considered a critical component required for testing ERL as the aerosol is passing through?

DR. RUSSELL: Some applications have included the mouthpiece. So the issue of whether or not you need to consider, you know, just the storage kind of components or the end-use components depends on the particulars of your product and what these materials are made out of and what the kind of contact time or any other conditions that might be pertinent to help assess the potential risks associated with the product.

CDR. RUSSELL: Thank you. We have another question from the virtual audience. How are exposure levels determined in the calculation of risk?

DR. WURCEL: Thank you for that question. I will answer it very briefly, and then I will ask the person who asked the question to pay attention to

Session 6 where this topic will be discussed more in-depth. Essentially, we will briefly look at the quantity that was detected in analytical studies and also consider some of the use parameters specific for that product. Again, there will be further information about this that is discussed in Session 6. Thank you.

CDR. RUSSELL: Opportunity for the in-person audience to ask any questions. Our virtual audience is not shy. Can the panel comment on the use of simulated versus actual e-liquids for leachable studies? Also, is one method preferred over the other?

DR. RUSSELL: Simulated e-liquids can help simplify the data analysis. So, for example, the e-liquid including your PG/VG, nicotine, any of the organic acids that might be the major -- oh, sorry. So I'll repeat. So using a simulated e-liquid, meaning that is an e-liquid that doesn't necessarily contain every single ingredient that's in the finished e-liquid, can help simplify the data analysis. So, for example, an e-liquid that includes the nicotine, the organic acids, the PG and the VG, these major

components, can provide really useful leachable study data. And the leachable study can be conducted alongside your stability study of your finished product, but they're not exactly the same study, right? There's a non-targeted analysis component, this investigating of things that aren't just on the HPHC list that needs to be considered in the leachable study data.

CDR. RUSSELL: We have another question from the virtual audience. Regarding the HPHC tests for tobacco molasses, we could not find any laboratory that applied it for tobacco molasses. For e-liquids, there are a lot when requesting such a test. There must be a reference for the type of test. Are there any available?

DR. CECIL: One of the problems in the discussion here is that molasses is a complex ingredient. It's not a single ingredient that we can look for. If there is not a method, then method development would need to occur, and it would be one of those requirements you'd have to work with that laboratory to ask them to do the development of the individual constituents within a flavor or an additive

component like molasses and then do the assessment of the quantities that are there.

CDR. RUSSELL: Thank you. Do we have any additional questions? If not, this -- oh, come on up, sir.

MR. FISHER: Hey, Michael Fisher from Juul. A question for Dr. Russell. You mentioned NTA analysis in the context of leachables, so I assume what you're talking about is screening that NTA for the presence or absence of those leachables. So that would be, would that typically be sufficient to determine if that leachable, if a leachable is likely to be an aerosol or not? Is that the kind of data that you would use to do that analysis?

MS. RUSSELL: Yes. So there's a relationship between doing an extractable study and doing an NTA, a non-targeted analysis, there and in the leachable study. So extractable studies are worst-case scenario where you're kind of bracketing the physiochemical properties of the e-liquids, for example, that are likely to be used in your product. And in the leachable, from the extractable study you would identify a potential leachable, so you can

target those things, but the extractable study doesn't necessarily give you all of the information, all the potential leachables, and so it's useful to include that type of analysis for the leachable study. And it's because these things are often at low concentrations, it's important to carefully prepare samples as discussed widely in the literature about how to prepare the samples and how to make sure your methods are developed well enough and things like this, that your methods are robust and sensitive and fit for purpose.

MR. FISHER: Thank you.

CDR. RUSSELL: Do we have additional questions from the audience? If we have no additional questions, this concludes our panel's session for Session 4.

With the conclusion of this session, we will now take a break, and we will break for approximately 15 minutes. And we will reconvene approximately 10:17. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:02 a.m. and resumed at 10:22 a.m.)

CDR. RUSSELL: For flavored ENDS PMTAs. Dr. Miller.

DR. MILLER: Good morning. My name is Dr. Mollie Miller, and I'm a health scientist at the FDA Center for Tobacco Products. Today, I'll be discussing recommendations for abuse liability studies.

I'm going to start with a high-level overview on abuse liability, including its role in the premarket tobacco product application review process. And then I'll discuss considerations when designing abuse liability studies to support PMTAs and provide a hypothetical abuse liability study design in commonly-reported measures. And, finally, I'll highlight the importance of product-specific information when evaluating abuse liability in PMTAs and considerations for bridging abuse liability data.

Abuse liability refers to the potential of a substance to result in addiction and to be used repeatedly or even sporadically, resulting in undesirable effects. The abuse liability of a new tobacco product is important for FDA to evaluate because it indicates the degree to which users of the

tobacco product are likely to use and develop addiction to the product. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For example, if a new product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. On the other hand, low abuse liability suggests that it's less likely that new users will become addicted to that product.

Specifically, FDA requires the submission of abuse liability information under its interpretation of Section 910(b)(1)(a) and (g) of the Tobacco Control Act because it indicates the likelihood of users to become addicted to the product and face the health risks posed by product use over the long term. As stated in the PMTA final rule, if a PMTA does not contain substantive information regarding the abuse liability of a new tobacco product, FDA may refuse to file the application. Further, if FDA lacks sufficient information regarding the potential abuse liability of the new product, it intends to issue a marketing denial order for the new

product.

When FDA evaluates the abuse liability of a new product, evaluations are based on the totality of information available to understand the abuse liability of the new product both independently and relative to other tobacco products with a known abuse liability. So, for example, combusted cigarettes, nicotine replacement therapy, or other tobacco products of the same class. The types of data that may inform an abuse liability evaluation could be wide-ranging and may overlap with data submitted elsewhere as part of the PMTA.

As stated in the PMTA final rule, while applications need to contain some amount of substantive information concerning abuse liability to be filed, the abuse liability of a new tobacco product is an important part of FDA's finding of whether permitting the marketing of the new product would be appropriate for the protection of public health. An applicant should consider conducting an abuse liability study if they do not believe there is sufficient existing data regarding their product.

The standard abuse liability study is a

double blind placebo-controlled within-subject study comparing several doses of a new product to a comparator product with a known abuse liability. While this is the standard study design, applicants may choose to modify the standard design to fit their needs for submission.

Abuse liability studies commonly include nicotine pharmacokinetic, or PK, outcomes as primary outcome measures in other abuse liability outcomes. So, for example, subjective measures, use topography, and physiological effects, as secondary or exploratory outcomes. These outcomes may be assessed under both prescribed and ad libitum or unrestricted use conditions.

Although we highlight a hypothetical abuse liability study in this presentation, it's important to note that other evidence included in the PMTA, so for example HPHC aerosol data that includes bridging to human use behavior or data on actual product use over time, may provide additional support for an abuse liability evaluation.

When selecting comparison products for abuse liability assessments, it's helpful to include a

comparison to both products that are within the same category or subcategory of tobacco product and to other categories of tobacco products currently on the market as appropriate. For open ENDS devices or e-liquids, the applicant should justify the e-liquid characteristics or devices used in the clinical study. The applicant should ensure that the study conditions, so that is the e-liquids and the devices, represent the market in what may be reasonably used with the new product. Justification may include sales or observational data on actual e-liquid and device used among consumers.

Additionally, comparison products should be chosen based on the intended user population. For example, a new nicotine pouch product may include a smokeless tobacco product or a combusted cigarette as the high abuse liability comparison product, dependent upon whether the intended user population are people who use smokeless tobacco or cigarettes respectively.

So here we provide a schematic that depicts a hypothetical abuse liability study comparing three different flavors of ENDS to a usual brand cigarette. In this study, we'll assume that the

nicotine concentration of each ENDS is identical. In this within-subject laboratory study, participants are first screened for inclusion and then randomized to the order in which they'll use each study product. A distinct product is tested at each of the four study visits, and each study visit is separated by at least 48 hours.

Prior to each study visit, participants are required to abstain overnight for approximately 10 to 12 hours from any nicotine or tobacco product use. At each session, participants use their randomly-assigned product under both prescribed and ad lib use conditions. Nicotine pharmacokinetics and pharmacodynamics are assessed prior to and after use of the assigned product.

The first phase of the study, or phase A, is a prescribed use phase. Because tobacco use behavior can vary widely among users and across products, in this phase, the puff number and timing are standardized to allow between subject comparisons. In PMTAs, it's important for applicants to justify the appropriateness of the chosen prescribed product use regimen in order for reviewers to determine if

it's representative of actual use behavior.

Ideally, the prescribed product use regimen should reflect a single unit of use. So, for example, 30 minutes of snus use, 10 ENDS puffs over five minutes, or 10 cigarette puffs over 10 minutes. The applicant may justify the chosen regimen with published literature, a puff topography study, or based on specifications of the device. So, for example, device activation is limited to a certain number of puffs or a certain duration.

In this phase, nicotine pharmacokinetics and subjective effects are assessed prior to and for three hours after using the assigned product. The three hours of PK sampling allows for adequate estimation of the area under the nicotine plasma concentration versus time curve and distribution elimination rate constant to be used for baseline correction.

The next phase of the study, or phase B, is an ad lib use condition which provides useful data on how various dimensions of use topography may fluctuate when product use is not controlled. That is, tobacco product use is typically adjusted by users

to deliver a preferred level nicotine, and this variability may lead to differences in PK measures and other outcomes between prescribed and ad lib use conditions. The absence of ad lib data may limit a reviewer's ability to draw conclusions on the abuse liability of the new product, particularly if data from prescribed use of the new product suggests similar abuse liability as the high abuse liability comparison product.

If an applicant chooses to omit an ad lib phase, they should provide scientific rationale and bridging data, if appropriate, to support this methodological decision. In this phase of the example study, nicotine pharmacokinetics, subjective effects, and puff topography are assessed prior to and during a period, so, for example, three hours, of ad lib use of the assigned product.

Again, it's important to note that the study described today represents a hypothetical abuse liability study design. As mentioned previously, applicants may choose to modify the standard study design to fit their needs for submission. Ultimately, applicants should provide justification for the

methodological decisions.

To go more in-depth on commonly-reported abuse liability measures, we'll start with nicotine pharmacokinetic parameters. Nicotine PK is used to evaluate the rate and extent of nicotine absorption from our product, and this is typically measured in blood plasma. These parameters characterize systemic nicotine exposure. Nicotine PK is dependent upon the user population, as well as product characteristics. So, for example, power and e-liquid nicotine concentration, which should be considered when designing an abuse liability study.

Commonly reported nicotine PK measures include Cmax, or the maximum nicotine concentration reached, Tmax, or the time it takes to reach Cmax, and AUC, or the area under the plasma nicotine concentration versus time curve.

Next, self-reported subjective effects. So, for example, drug liking, satisfaction, craving and withdrawal, are widely-used measures in reinforcing efficacy and abuse liability for drugs. These measures are typically reported on a bipolar visual analog scale and used during drug self-

administration studies. Generally, tobacco products with greater positive subjective ratings have greater abuse liability. Measures of relief from craving and withdrawal also reflect addiction potential and are associated with current and future tobacco product use, including the likelihood of switching. And, finally, use topography provides a quantitative measure of use behaviors. So, for example, number of puffs, puff volume, and duration. And this can be used to evaluate compensatory behavior, so that is changing puff topography to achieve a desired nicotine delivery.

It can also be used to assess differences in behavior across products and populations and to inform human exposure in aerosol emissions testing for nicotine and other HPHCs. Several smoking topography instruments have been modified to measure the topography of newer tobacco products such as ENDS. Although self-report and video recordings can be used to measure puff topography, their utility is limited based on low reliability and validity of self-report and incomplete topography metrics that can be collected from video coding.

When selecting a participant population for an abuse liability evaluation, it should be properly justified and it must be one in which the positive control or the high abuse liability condition will test unequivocally positive. For example, if the intended user population for a new ENDS product is adults who smoke combusted cigarettes, then the sample should include participants who currently smoke cigarettes because combusted cigarettes is the most appropriate positive control. Participants are typically adult users of either the category of new product, so, for example, ENDS, and/or regular users of the comparison product, for example, combusted cigarettes.

The study design should incorporate inclusion criteria around product use, so, for example, the length of time participants have been smoking cigarettes and how many they smoke per day, to ensure generalizability. It's also important for the applicant to consider how prior experience with the study product or product category or lack thereof may affect interpretation of study outcomes, such as use topography, subjective measures of abuse liability, as

well as exposure to nicotine and other HPHCs. For example, data show that experienced ENDS users can modify their behavior over time by taking longer and larger puffs to obtain more nicotine from the same ENDS compared to ENDS inexperienced cigarette smokers, and this impacts the abuse liability of the products.

Applicants may also include a familiarization period in which participants are allowed to use the study products for a period of time prior to undergoing nicotine pharmacokinetic assessments. Although user adaptation may take several weeks, the use of even a limited familiarization period facilitates some degree of acclimation to use of the product.

So as mentioned earlier, the abuse liability of a new ENDS product is influenced by the combination of device and e-liquid characteristics, such as device type; nicotine formulation, so, for example, nicotine freebase or salts; nicotine concentration; and e-liquid flavor. As such, product-specific information, that is data from an abuse liability study using the new product, typically serves as the strongest source of information for an

abuse liability determination of the new products.

If an applicant submits data from a clinical study that used precursor products or products with different characteristics than those of the new products, the applicant should explicitly bridge the study products to the new products to permit an abuse liability evaluation. It's also helpful for the applicant to clarify in the PMTA if the products used in the clinical study are identical to the new products.

So below is a hypothetical where an applicant tested a previous version, or version one, of their ENDS products than the one that's included in their PMTA, which is version two. Version two added a child safety lock, but the rest of the characteristics were similar. The applicant wants to bridge the results from their abuse liability study conducted with version one products to version two products because they have no clinical data for their version two products. So they bridge version one to version two by showing that most device characteristics, so, for example, power and coil resistance, and e-liquid characteristics, for example, nicotine concentration

and flavor, are the same and by providing machine-generated aerosol data showing the nicotine and non-nicotine HPHC aerosol profiles are identical between the two devices.

While product-specific information permits the most rigorous abuse liability evaluation, if an applicant chooses to bridge data from a study tobacco product to additional new products, including products with different nicotine concentrations and/or nicotine formulations, characteristics, and flavors, the applicant should provide scientific rationale and justification to support bridging.

With regard to nicotine, the level of nicotine in a tobacco product may affect how the product is used. So, for example, the use topography, the frequency of use, and the amount consumed. And it, therefore, may influence dependence and HPHC exposure. Testing only a subset of nicotine concentrations, so, for example, only the highest nicotine concentration or only the highest and lowest nicotine concentrations, may produce nicotine exposures and subjective effects that are not representative of the abuse liability and behavioral

effects under the range of nicotine concentrations of the new products. Therefore, applicants may be able to test a subset of nicotine concentrations when conducting clinical studies to assess abuse liability, so, for example, a low, a medium, and a high nicotine concentration, and then bridge the data to all nicotine concentrations in a product line.

In the hypothetical here, an applicant included 15, 30, and 50 milligram per milliliter nicotine concentrations of a tobacco-flavored ENDS in their abuse liability study, and then they bridged the results to 20 and 40 milligram per milliliter doses in their product line.

Similarly, when bridging across flavors, applicants should consider how the various flavors and flavor constituents in the new products may impact use behavior and, thus, may influence a user's exposure to nicotine and other HPHCs. They should also consider the possibility that subjective measures of abuse liability may differ for each new product, including those that will be tested in the clinical studies and those that will not be tested.

In this below hypothetical, an applicant

tested tobacco, menthol, and blueberry-flavored ENDS of the same nicotine concentrations in their abuse liability study. They compared the nicotine PK, subjective effects, and topography of the three flavors to describe variability in these outcomes as a function of flavor and how this variability compared to data from the comparison product. They bridged the results to watermelon and mint ENDS from their product line by assessing machine-generated nicotine HPHC aerosol yield from all of the flavors and they included justification for how the puffing regimen for the aerosol data is comparable to actual use via a topography study.

They also provided an actual use behavior study showing that the frequency of product use is similar across tested and untested flavors. Again, this represents one hypothetical bridging approach that may not be applicable for all applications.

And, finally, applicants may choose to bridge from published literature to their new products to support an abuse liability evaluation. Once again, it's important to note that applicants should provide explicit rationale and justification as to why the

products used in a published study can be bridged to the new products, taking into consideration the many product-specific and individual characteristics that influence abuse liability. Applicants should identify a bridging product or products that are characteristically similar to the new products. So, for example, just considering device power or wattage is likely not sufficient without taking into consideration additional characteristics that may influence abuse liability, such as nicotine concentration, presence of nicotine salts, and flavor.

So in summary, the abuse liability of a new tobacco product is important for FDA to evaluate because it indicates the likelihood of use and degree of addiction to the product. FDA's abuse liability evaluations are based on the totality of information available in the application. Product-specific information typically serves as the strongest source of information for an abuse liability determination of the new products. Applicants should design abuse liability studies with consideration of comparison products, intended user population, and methodological constraints. And, finally, applicants should provide

explicit justification to support bridging for any proposed new products that are not evaluated in a clinical study.

So I'd like to thank you for your attention, and we'll save all questions for the panel following this session.

(Applause.)

DR. ALEXANDRIDIS: Okay. Hello. Good morning. My name is Apostolos Alexandridis. I'm a health scientist in the epidemiology branches in the Division of Population Health Science in the Office of Science at CTP, and I serve as an epidemiology reviewer and a technical project lead for the PMTA pathway, as well. And today I'll be discussing some study design and analytic considerations related to the assessment of adult benefits of flavored ENDS products in PMTAs.

So I'll start my presentation reviewing some of the relevant background on PMTAs and the framework that CTP uses to evaluate the risks and benefits of flavored ENDS products. And, next, I'll cover two different types of study that can be used to evaluate those benefits, and those are clinical trials

that are reviewed by behavioral and clinical pharmacology, or BCP, and cohort studies that are reviewed by epidemiology.

So as we've learned over several sessions of this meeting, the APPH standard is the regulatory standard for the PMTA pathway, and OS is responsible for making that assessment during product review. And the APPH standard is a whole-population standard, meaning that our reviews consider people who would or would not use a new product, whether people currently using other tobacco products would stop using those products or switch to the new product, and, in particular, if people not currently using any tobacco products would use the new products. And that last part is a key consideration because of youth risk, and youth risk is a key consideration in product review for a few reasons. So, firstly, most initiation of tobacco products occurs during adolescence with almost all initiation happening before age 25. And, secondly, although tobacco products that are reviewed under the PMTA pathway do have the potential to be less harmful than cigarettes, they are not without harm. And in the case of ENDS, such as e-cigarettes,

there are still many unknowns about long-term risks.

So FDA has concluded that, for non-tobacco flavored ENDS, there is a known and significant risk of youth appeal, uptake, and use, and this risk is well documented in the literature, as well. And the risk applies to all non-tobacco flavored ENDS, including menthol-flavored ENDS. So, therefore, in PMTA review, we use the term flavored ENDS to refer to any ENDS product with a characterizing flavor other than tobacco, and I'll be using that definition today, as well.

Based on findings from the 2022 National Youth Tobacco Survey, or NYTS, more than 80 percent of youth currently using ENDS products report using flavored ENDS products. And youth ENDS users are more likely to report using flavored products compared to adult ENDS users. And flavored ENDS also facilitate initiation and ultimately promote transition to regular use.

Although youth ENDS use has declined from its peak, it does remain relatively high among youth, especially compared to combusted tobacco products. Therefore, there is a high burden of evidence needed

to demonstrate that the marketing of a flavored ENDS is APPH, specifically potential benefit for adults. So we, therefore, arrive at this issue of adult benefits of flavored ENDS products.

No ENDS product has yet been approved by CDER as a smoking cessation therapy. However, there is a growing body do evidence that suggests that ENDS can contribute to transitioning away from cigarettes. And one example in the literature is the Cochrane Tobacco Addiction Group in the UK who systematically reviewed the available evidence on this topic, and concluded there is high-certainty evidence that electronic cigarettes containing nicotine increased smoking cessation as compared with nicotine replacement therapy.

Flavored ENDS are known to be broadly appealing to and widely used by adult smokers, and this appeal may promote more frequent use and switching. But at present, limited data and mixed findings regarding flavored ENDS give us far less certainty about their benefits as a category for switching and cessation.

In reviewing PMTAs for flavored ENDS

products, FDA reviews for robust and reliable evidence of their products benefits for adult smokers. In particular, this means evidence that their flavored products are likely to promote complete switching or significantly-reduced cigarette smoking in adults beyond that of tobacco flavored ENDS. FDA also reviews for product-level specificity because ENDS are highly varied in their performance characteristics, and this directly impacts nicotine delivery.

The need for this evidence of added adult benefit is specifically due to the known risks of flavored ENDS products for children and young adults under 21. By contrast, tobacco-flavored ENDS raise a different set of considerations because they do not pose the same degree of youth uptake.

ENDS products themselves, though, are one piece of the puzzle in determining population-level uptake and risks. Advertising and sales are another closely-linked component. However, FDA has concluded that current approaches to sales access restrictions on their own do not sufficiently mitigate the substantial risk of flavored ENDS to youth.

There are also, however, novel mitigation

measures, such as device access restrictions, that may provide more substantial mitigation of these risks. And one example may be age-gating technologies using biometric user identification or similar approaches to unlock and use a product. The use of these approaches in the current marketplace is limited, however, and FDA continues to assess them.

To recap then, FDA reviews specific evidence of added benefit of flavored ENDS to adult smokers. The two types of evidence most likely to demonstrate this added benefit include experimental evidence from randomized control trials, or RCTs, as well as observational evidence from longitudinal cohort studies or actual use studies. FDA would also consider other evidence that reliably and robustly evaluated the impact of the new flavored versus tobacco flavored products on switching or significant cigarette reduction over time among adults who smoke.

At present, we conduct targeted review of PMTAs for flavored ENDS to determine if evidence might be capable of showing an added benefit to adult smokers of flavored ENDS or if other evidence on novel or materially different mitigation measures are

present. If so, the application proceeds to full scientific review for evaluation of the other components required for an APPH determination.

Evidence of added benefit is evaluated to determine if potential benefits would outweigh the significant risks to youth such that marketing the flavored product would be APPH. So one approach that applicants can take to demonstrate the adult benefit of a new flavored ENDS product is to conduct a randomized control trial, or an RCT, using the new flavored ENDS product. In the context of tobacco product applications, an RCT is a study in which participants from a target study population are assigned randomly or with equal chance to experimental conditions involving the new products or controls. Resources, such as CDER's Guidance on Developing NRT, which was updated earlier this year, or the published literature on best practices in smoking cessation trials, while intended to assist in the development of cessation therapies, can also be useful to applicants when designing a trial to demonstrate the adult benefits of flavored ENDS. Additionally, there are many well-established frameworks, such as the consort

statement, that can ensure clear reporting of design, analysis, results, and conclusions for randomized trials.

This diagram here provides an illustration of a possible RCT design. Participants are recruited from the desired study population, such as current established smokers, and randomly assigned to a study condition, such as using one or more flavored ENDS products, one or more tobacco flavored ENDS comparators, or even a control condition based on the study aims. Throughout the study, outcome measures, such as combusted cigarette abstinence, can be collected and compared between the groups.

DR. ALEXANDRIDIS: With the appropriate sample size, randomization of participants in clinical trials minimizes measured and unmeasured confounding, and the potential for preferential assignment in studies. Further, the RCT study design provides a basis for performing standard pre-specified statistical analyses and hypothesis tests.

These analyses typically allow for causal inference about the impact of adopting a new product. In this case, the added benefits of a flavored ENDS

product over a tobacco flavored ENDS comparator on the outcome of cigarette smoking cessation. These conclusions can inform FDA's assessment of added benefits for new flavored products.

A key first step in designing an RCT is to determine the study population from which participants will be recruited. When determining the study population, FDA reviews for the intended user population of the applicant's new products, and scientific rationale for the selected study population that the applicant chose to sample.

For an RCT studying adult benefits of flavored ENDS products, if evaluating potential benefit to adult smokers, the study population should consist of adults who smoke combusted cigarettes who are not currently seeking treatment for smoking cessation. Participants may also include adults who use other tobacco products, including ENDS.

Additionally, applicants may consider assessment of potential residual confounding variables as numerous baseline factors, including ENDS use history, daily cigarette consumption, nicotine dependent severity scores can impact primary study

outcomes. This assessment can support mean comparisons or standardized mean differences to demonstrate balance across study arms after randomization.

Applicants may also consider establishing eligibility criteria or stratifying the sample to better account for those variables. And as noted earlier, published resources on best practices in smoking cessation trials may provide useful considerations on the tobacco use variables that may influence outcomes. And finally, statistical methods can also be used to control for these variables when other methods are not feasible.

And whichever approach is taken to control for confounding variables, the FDA reviews the scientific rationale and justification for those methods, and the baseline variables that they attempt to control for. Appropriate experimental conditions and randomization procedures are essential for designing an informative RCT.

The study design employed in an RCT may vary across applications according to the number and variety of products included. But scientific

justification and rationale for the study design and the randomization procedure should be provided in the study protocol. And the study should be prospectively designed, and statistically powered to evaluate changes in the primary outcome measures.

For applications involving flavored ENDS products, FDA looks for participants to be randomized to use a tobacco flavored product, or the flavored product, or each of the flavored products if multiple flavored products are to be tested. In applications with multiple flavored ENDS each product might be tested, or some products might be tested, and then untested flavored products are bridged to the tested flavored products.

If participants are assigned to a combined flavor product condition, participants self-select their preferred flavored product for use throughout the study duration. This approach may yield uneven sample sizes across the different flavored products tested. Some of which may be too small to permit an evaluation of any added benefit associated with use of those flavored products that are not chosen by participants.

Ultimately, FDA looks for applicant to justify the approach taken, to analyze data from a combined flavored product condition, and how the analysis can support FDA's evaluation of each flavor. Should a control condition be incorporated into the study design, applicants should consider which comparisons are most informative for their new products.

For example, applicants may consider randomizing control participants to receive no further guidance, allowing for a contrast with spontaneous smoking cessation using any modality. Or control participants could receive NRT, which would allow for a comparison of effectiveness on study outcomes between the new products and NRT.

When randomizing participants to study conditions, interacting with participants, and analyzing study results, efforts should be taken to enforce blinding, which refers to limiting knowledge of intervention assignment without jeopardizing the study objectives. Blinding can be difficult in studies with tobacco products, but helps reduce bias and expectancy effects particularly among

investigators and staff involved with data collection and data analysis.

Applicants may also consider instructing participants in the ENDS conditions to switch completely to the study products on the switch date, and refrain from smoking combusted cigarettes for the remainder of the study. Regardless of whether participants are explicitly instructed to switch to study ENDS products, applicants may consider supplying participants with their assigned study products at regular intervals throughout the study, for example weekly, or monthly.

This would also include supplying other products, such as NRT, to participants in a control condition if used. Applicants may also consider adding a grace period prior to the start of the experimental condition or official switch date. And this approach allows for participants to acclimate to their new products, and sample different flavors of ENDS products if the RCT design allows for that selection.

Applicants may consider scheduling intermittent assessments throughout the study duration

with participants throughout the study -- with those assessments including self-reported daily cigarette consumption, study product use, dependent severity, and combusted cigarette exposures. The frequency of these visits may vary according to study duration with more frequent visits in shorter duration studies.

FDA does not recommend a specific length of RCT studies in determining added benefits of flavored ENDS. FDA looks for the clinical study duration to be appropriately justified based on the outcomes being investigated. In RCTs evaluating adult benefits of flavored ENDS products, outcomes of interest, such as combusted cigarette abstinence occur gradually over time.

Therefore, studies will likely need to evaluate behavior over extended periods as well. Published literature has recommended six months as a standard follow up duration for assessing differences in smoking abstinence between experimental conditions allowing for an evaluation of lasting behavior changes.

However, FDA also acknowledges that RCTs less than six months may also inform the assessment of

added benefits of a flavored ENDS product. Whatever study duration is chosen, FDA reviews for the scientific justification in the study protocol. Moreover, given that short term abstinence is unlikely to confer health benefits, and is often associated with relapse, RCTs with follow up periods less than four weeks may not be sufficient to provide robust evidence of behavior change.

In general, for RCTs, the primary study outcomes are defined a priori. For example, the primary outcome may consist of the proportion of participants who are abstinent from combusted cigarettes based on self-report or biochemical verification such as breath carbon monoxide. That said, evaluating with in subject changes in certain outcomes from baseline to study end can also inform review of new products.

We also acknowledge that strict abstinence end points may not be appropriate for all study durations. For lengthier studies, such as those lasting six months or longer, applicants may consider allowing a limited number of cigarettes while participants transition to ENDS. And for studies of

shorter duration, applicants may consider stricter abstinence end points.

To minimize recall bias, applicants may consider assessing self-reported tobacco use daily, including study and non-study product use. Methods can include use of written or electronic daily diaries, or interactive systems that call or text participants at the end of each day. Common secondary outcomes include daily cigarette consumption, the longest period of combusted cigarette abstinence, and seven day point prevalence abstinence.

Which is defined as the percentage of participants remaining abstinent in the previous seven days. Less common secondary outcomes have included risk of relapse, reduction in smoking related withdrawal, or reduction in urge to smoke or dependency scale scores. Applicants should provide scientific justification and rationale for whichever outcomes they chose, and how they define them.

RCTs evaluate to the impact of an intervention, in this case, product use over time. As described previously, applicants may consider collecting baseline measures at the start of the study

that can later be compared throughout the study to provide additional support for FDA's evaluation.

Given the generally smaller sample sizes compared to large, observational studies, RCTs do provide a useful opportunity to collect the baseline measures such as biomarkers of nicotine and combusted cigarette exposure such as urinary cotinine, and expired CO. Combusted cigarette use behavior such as daily cigarette consumption and dependent severity such as the Fagerstrom Test for nicotine dependence.

As with any outcome measures or study design parameters, one consideration is again, the scientific rationale and justification for those measures. As I said before, the CONSORT statement is used worldwide to improve the reporting of randomized control trials, and may be useful for applicants who choose to conduct RCTs.

Once the RCT is completed and data are collected, there will likely be missing data from participants who either miss study visits, or did not complete a study. The protocol typically describes strategies that are planned to minimize missing data, how missing data will be handled, and how the selected

statistical procedures incorporate issues relating to missing data into the analysis plan.

Best statistical practices for handling missing data typically consider the objective of the study, anticipated missingness, assumptions associated with missing mechanism, missing at random for example, and actual observed missingness. The intent to treat, or ITT population, in which every participant who is randomized to a condition is included in the analysis regardless of study completion status or protocol adherence is considered the gold standard for RCT analyses to preserve randomization, maintain sample size, and reduce bias.

Generally, in a trial study with closely spaced study visits, the applicant can consider a participant abstinent for a single missing visit if the participant had documented, confirmed abstinence before and after the missing visit, and then later self-reports abstinence at that time. The applicant may consider the participant non-abstinent if the participant misses two or more consecutive visits during the study.

Or if the subject withdraws from the

study, regardless of smoking status at the time of withdrawal. Results from the protocol population are the participants who completed the full study and were adherent to study products can also be analyzed and presented in parallel with the ITT population. Today we'll also be characterizing the observational studies that can be used to assess the adult benefits of flavored ENDS products such as cohort studies and actual use studies.

These cohort studies have all the usual advantages and disadvantages compared to trials as we would expect. Very large samples of participants, hundreds or even thousands in fact are readily attainable. They are cheaper to conduct, and they can provide real world evidence within a purchaser or user population.

But as we'll discuss, they carry a high risk of missing data, and confounding. But we should note that this is not the end of our discussion and dialogue with stakeholders on these issues, and there are many ways to conduct high quality cohort studies. Just as with the CONSORT statement for RCTs, the strobe statement for observational studies can also

provide guidance on the conduct and reporting of high quality studies, for example.

In many settings of observational studies, good study design can be guided by outlining the idealized RCT that you would like to conduct, and then designing both a study and analytic approach to best approximate that RCT. Just like in an RCT, the cohort study samples and enrolls participants from the source population of interest, but without the many benefits of randomization.

FDA reviews, baseline data collection, including detailed demographics, and baseline tobacco use assessments, in order to address potential confounding and appropriateness of the study sample. Additionally, tobacco product use in a cohort study is determined solely by the participant, and can vary over the time period. Therefore, accurate assessments of all tobacco products used across the entire study period are critical.

Generally speaking, actual use studies of tobacco products submitted in PMTAs may seek to broadly capture all users of a given product. In terms of those users' use behaviors, this can include people

who currently smoked, formerly smoked, never smoked, use or used other forms of tobacco, or have never used tobacco at all.

However, to address specific evidence of added benefits of flavored ENDS in adults who smoke, we have looked at the sub population of current established smokers. And this has typically been defined as any past 30 day smoking with over 100 lifetime cigarettes smoked, but other definitions may also be appropriate depending on other aspects of the study, such as the recruitment.

Participants in cohort studies can be recruited based on new or current use of specific ENDS products, or based under current tobacco use, and then provisioned with study ENDS products after their enrollment. And this latter approach is also called an actual use study, and allows for observational studies to be conducted with products without marketing authorizations.

Although not strictly observational, this approach does allow for follow up in a more naturalistic setting than an RCT. But regardless of the approach that's taken, diverse forms of

recruitment may be useful to recruit similarly diverse cohorts of participants who use ENDS. These can include in package invitations in retail or online sale settings, market research panels, social media outreach, or messaging apps.

If a company uses multiple channels for sales or outreach, an appropriately justified pooled analysis of participants recruited through multiple channels may also be particularly useful. As I described previously, observational studies generally offer much greater ability to recruit large numbers of participants compared to RCTs.

Sufficient sample size is critical for observational studies of flavored ENDS. FDA reviews for evidence that applicant's cohort studies are sufficiently powered for robust significance testing, or regression models used. Typically cohort study participants do not receive additional guidance on their tobacco use behavior.

Those behaviors will often be very dynamic compared to RCTs. People using ENDS may try different flavors of a product, rotate between one or more flavors for more usual use, and so forth. Follow up

assessments throughout the length of the study should accurately assess these changes in use of flavored products over time.

Current established smokers in particular may also be using other tobacco products in their efforts to reduce smoking, switch, or quit, and they also use approved cessation therapies such as NRT, or non-NRT medication. Use of any of these products should also be assessed, as they may be potential confounders, and stratified or adjusted analyses may be necessary for unbiased estimates of the flavored ENDS products.

In order to establish any additional effect of flavored ENDS over tobacco flavored ENDS, an appropriate tobacco flavored ENDS comparator and justifications for their use should be used, preferably in the same study as the flavored ENDS products. This is particularly important if an applicant does not market a tobacco flavored ENDS product, and intends to rely on other tobacco flavored ENDS products as their comparison product.

Just as with RCTs, FDA does not recommend a specific length of cohort studies in determining

added benefits for flavored ENDS. However, longer duration studies typically enable stronger conclusions regarding the long term behavior changes. Whatever study duration is used should be justified with appropriate literature, and based on the primary outcome, for example, complete switching.

In all studies, efficiency may be increased by emphasizing more frequent follow up in earlier months with less frequent follow up in later months. Complete switching, and significant reductions in smoking are the most typical primary and secondary outcomes of interest in studies of flavored ENDS, cohort studies I should say, of flavored ENDS.

Complete switching is typically defined using past 7 day or past 30 day abstinence. Longer studies of six months or more duration may also consider a maximum allowable number of cigarettes, similar to our guidance on clinical trials. Additionally, applicants may also pool complete switching and complete cessation of all tobacco products into a secondary end point of total smoking cessation.

Significant CPD reduction is another

outcome in cohort studies. CPD may be reported as both a binary and a continuous outcome, and when reported as a binary outcome, the threshold value that is used, for example 50 percent and 75 percent, should be justified in the application narrative with the supporting literature.

FDA reviews both descriptive and inferential analyses provided in cohort studies. Regression analyses can be used to address repeated measures, confounders, and FDA also reviews for the rationale behind any sensitivity analyses that are provided in the study. Study results are also evaluated for internal validity.

With multiple points of follow up available in a longitudinal study, FDA reviews findings in trends or outcomes, for example, to see if they are interpretable and consistent over the duration of the study. And if model estimates are plausible and interpretable under similar model specifications. Finally, an extremely critical issue in cohort studies is loss to follow up and the handling of missing data in the studies.

Any approaches for imputation that are

used should be justified. Additionally, missing as smoking coding that imputes all participants lost to follow up as smoking cigarettes only may be considered as an additional conservative estimate of the main effects of flavored ENDS products. Thank you for your attention and interest today, and I would like to thank my colleagues for their collaboration and thought in developing this presentation.

And if you have questions, I encourage you to ask them now at our panel discussion. Thank you.

CDR. RUSSELL: Thank you both for your presentation. We will now begin our panel session for session five. As a gentle reminder, please ensure that your questions are related to the topic discussed during the session. Our panelists for this session include four panelists. We have Dr. Benjamin Apelberg, Dr. Apelberg serves as the deputy director for regulatory science in the Office of Science at FDA Centers for Tobacco Products.

In this role, he oversees the Office of Science's scientific divisions responsible for managing the Office of Science's regulatory research program, scientific reviewers that serve as TPLs, who

work on PMTAs, and MRTPA pathways. In addition, he gives supervision to staff who provide scientific expertise in the field of health sciences, medicine, pharmacology, epidemiology, social science, evaluation, and statistics to support the center's tobacco product regulatory efforts.

Dr. Apelberg joined CTP in 2010 as an epidemiologist, and sequentially served as epidemiology team lead, branch chief, and director of the Division of Population Health Sciences. Before serving in his current position, Dr. Apelberg has a PhD in epidemiology from John Hopkins Bloomberg School of Public Health.

Prior to joining FDA he served as a faculty member at John Hopkins University. Welcome, Dr. Apelberg. Dr. Miller is a senior health scientist in OS' Division of Individual Health Sciences. Dr. Miller joined CTP as a pharmacology reviewer in 2018, her focus is on evaluating the abuse liability of tobacco products, particularly as it relates to pre-market tobacco application review.

In addition, she is a scientific expert in the field of addiction and behavior pharmacology of

tobacco, and is a primary investigator on multiple clinical studies designed to fill gaps in tobacco regulatory knowledge. Dr. Miller serves, and also provides a scientific support for regulations evaluating the knowledge basis for regulatory decisions, and drafting language used in tobacco product standards.

Prior to working at CTP, she was trained in behavior pharmacology at the University of Vermont, and completed a post doctorate fellowship at Brown's University Center for Alcohol and Addiction Studies. This is where she completed a 12 month tobacco regulatory science fellowship, and it was sponsored by the National Academy of Medicine at FDA. Welcome back, Dr. Miller.

Dr. Apostolos Alexandridis, Dr. Alexandridis is a health scientist in the epidemiology branch within the Office of Division of Population Health Science. In his current role he serves as an epidemiology reviewer for the PMTA pathway, as well as the technical project lead for the PMTA pathway. Dr. Alexandridis joined CTP in 2020 after completing an ORISE fellowship in Cedar.

His prior background is in substance use, and in injury epidemiology, and pharmacoepidemiology. Welcome back, Dr. Alexandridis. Last but not least we have Dr. Megan Shroeder. Dr. Shroeder is a supervisory pharmacologist in the Division of Individual Health Science in the Office of Science. She joined CTP in 2012, and has served as the behavioral and clinical pharmacology reviewer until she moved into her leadership position in 2016.

In her current role, Dr. Shroeder leads a branch of behavioral and clinical pharmacology reviewers who evaluate the abuse liability of tobacco products. She also co-leads PMTA technical project leads, and serves as the TPL in several PMTAs. Before joining CTP, Dr. Shroeder was trained in neural pharmacology at Georgetown University, and completed a post doctorate fellowship at NIH. Welcome, Dr. Shroeder.

Let's now begin with our first question. We will start with the audience. Again, we will do a two to two ratio. If we have any questions from the audience, please come up.

MR. CHAUDHARY: Hi, good afternoon, it's

Nveed Chaudhary from Broughton Life Sciences. Fantastic presentation, particularly the last one, Dr. Alexandridis, but I have a question. We heard quite a bit yesterday, and you yourself mentioned it today around educating technology. And I'm just wondering, would you say that for such novel technology, the focus of the application, and the focus of the APPH standard really moves away from your perception and intention to use studies, and the RCT studies that you described?

In terms of comparing the tobacco flavor to other flavors, towards really demonstrating the robustness of the educating technology instead? Do you think there's a shift if that technology was going to be present in products?

DR. APELBERG: I'll start with that, thanks for the question. You know, what Apostolos presented was really the framework that we've been using to evaluate flavored ENDS because of the particularly high risk for youth initiation. And as he indicated, we do believe that there are the potential for novel technologies, like age gated technology embedded in a device that could mitigate

that risk.

To your point, specifically, if it can be demonstrated that it really works effectively, and can't be disabled, or disarmed so that obviously it would be an important part of that evaluation, we still though, would want to -- the APPH determination is about risks and benefits, right? And so, the benefits in this case would still be with respect to users of more harmful products migrating to this product, so switching.

So, we'd still want to see evidence of that switching, but we have indicated that the level, the magnitude of that benefit wouldn't necessarily be as great if there were effective ways that have been demonstrated to really mitigate that risk.

MR. CHAUDHARY: And I know this is kind of a silly setting to make, but if we had a magic wand today that could get rid of all youth access issues, youth cannot use the product, the type of studies that you describe in terms of trying to demonstrate an additional benefit of flavors over tobacco flavor would not be required because there is no youth issue.

So, I guess what I'm saying is if we can

bring in technology which close to eliminates the ability for under age kids to use the product, are those RCT type of studies still required?

DR. APELBERG: You're speaking specifically with respect to the comparison to the tobacco?

MR. CHAUDHARY: Yes, yes.

DR. APELBERG: Yeah, I mean that evidence that we're looking for of added benefit is really a function of the higher risk, right? So, if you can demonstrate, you know in a way that we're confident can really effectively mitigate that risk, then we'd still be looking for evidence of benefit, but not necessarily that same kind of magnitude, or that same relative benefit.

MR. CHAUDHARY: Thank you very much.

MS. ZDINAK: Hello again, Jessica Zdinak, and very nice presentation, I really appreciated your perspective, it's very timely. I'm just going to put a plug in, but the RCT study on flavors versus tobacco actually we're presenting tomorrow at FDLI, so it was an amazing presentation to see that parallel. I do have a few questions though, tied to the instructions

to switch that you were mentioning.

When you're instructing them to switch, and making them switch, and how that parallels to actual behavior in real life -- so, I'm not necessarily industry, but as industry, I think we struggle sometimes with the laboratory setting of research in an RCT coupled with actual real life behavior, and how we can make sure we have external validity that what we see in switching is actually going to happen in real life, while also keeping the internal validity of the experiment.

So, the instructions to switch, having them there, and also the dynamic use of flavors you mentioned, and of course you're controlling things for the RCT, but don't you also want to know that your results are going to be generalizable when they leave the lab? And so, if they switch, and flavor use is dynamic within a study, don't you want to know that?

So, that when they leave the lab, they continue switching, and no longer using combustible cigarettes? And so, how could you combine approaches of the lab with real life, and how would you recommend us considering that when we design and give you this

reliable and robust data to make your decisions?

DR. APELBERG: I'm happy to start. You raise a really important point, I think that we recognize the sort of tradeoff between a more kind of controlled study versus a real world one. I mean, there's an additional complexity in that, if a product is truly a pre-market product, you're not going to really have real world.

I mean, you could do a study, like an actual use study where you give people the product, don't tell them how to use it and observe the behavior and what kind of behavior change occurs, so that's kind of one design. The other that Apostolos was talking about is more typical trial, where you're really instructing people to kind of get the ideal circumstances.

You know, what would be the impact. And so, I think we recognize that there's no sort of perfect crystal ball for predicting with 100 percent certainty what would happen in the real world. But we sort of look at the totality of evidence to try to make that determination.

MS. ZDINAK: Thank you.

CDR. RUSSELL: Thank you for your question. Sir, I want to acknowledge that I see you in the background, and I'll read the first two questions that came in, and you'll be next. And I'm going to -- we had a question that came in from the face to face panel, but I'm going to paraphrase this, and modify a little.

Is an applicant allowed to use clinical studies made by other organizations such as universities or government agencies as long as the product mirrors their particular product?

DR. SHROEDER: Yeah, so I think this is talking a little bit about bridging to literature. And a really key component of bridging is knowing how similar your product actually is to that bridging product. Some limitations with literature that we know is that they don't really accurately characterize their products often in some of the studies that are published.

And so, when you're trying to bridge your product, we've talked about some of these product characteristics, such as a specific nicotine concentration, presence of salts, power, device

wattage of your product, there's a lot that goes into bridging a product to a product that's in literature.

So, I'm not saying that it can't be done, but I'm saying pay attention to those product characteristics of the literature when making the determination of whether you want to use that literature to bridge.

CDR. RUSSELL: Thank you. The second question comes from the virtual audience. What would FDA's recommendation be in terms of blinding an abuse liability study given that it would be difficult, for example, to blind a combustible cigarette and an ENDS product? Or between different flavors of ENDS? Or does the recommended blinding not apply to such studies?

DR. SHROEDER: Yes, I think Apostolos covered that a little bit when he was talking about the RCTs, and kind of the same idea applies. So, for abuse liability, a lot of the underlying principles originally came from drug studies, where it was a lot easier to blind in those studies. For tobacco products, it's just natural that it's going to be harder to blind these products.

So, it's going to be obvious if they're using a cigarette, or if they're using an ENDS product. Once they're in the lab, and they're using an ENDS, if it's a flavored product, it's going to be kind of obvious what flavor that is. We acknowledge that, we recognize that, and we're saying to the extent possible try to blind the study.

Some considerations could be blinding the staff that goes in to administering these products. It's easy to blind the statisticians, and the technicians that are actually doing the analyses, it's also important to blind the primary investigator and the sponsors of the study.

So, while you may not be able to blind the participants, there's other forms of blinding that can go on with these studies.

CDR. RUSSELL: Thank you. We have a question from our audience.

MR. FISHER: Thank you, Michael Fisher from Juul again. Thank you both for your presentations, very nice. This is a question for you, Dr. Alexandridis, if I got that right, or close. You talked a lot about statistical power, and making sure

your study was big enough to show you what you need. It's helpful to know what effect size you're looking for in making that calculation.

Could you tell us that? Because, I mean, that is a really important question I think we all have. You talk about this weighing, what are the weights? Thank you.

DR. ALEXANDRIDIS: So, that's a very good question. We do want to see evidence of added benefit. So, the added benefit in that contrast between a flavored product and tobacco would need to be above zero as a baseline. But furthermore, the evaluation of that benefit then comes back to the overall valuation of the risks of the product, including the balance against non-users, or youth in particular.

So, those signals are always evaluated alongside each other. Ben, did you want to add anything?

DR. APELBERG: Yeah, sure, I'll just add on to what he's saying. I mean, we don't -- there's not a specific threshold at this point for sort of what that additional benefit should be. The reality

is the evaluation is multi-dimensional, because we're assessing not just the risks of youth initiation and the potential benefits to smokers or other tobacco product users.

But we're assessing the relative toxicity, and we're assessing other factors that also play into that overall evaluation. So, it's not really feasible to distill it down to okay, if you hit above this threshold you're a yes. But you can understand sort of wanting more clarity, and I will say too, I think as we talked about before, you're working on designing a particular study for a given product, we're happy to meet with you.

And sort of provide feedback on the design, including what goes into estimating sample size, and so forth.

MR. FISHER: Thank you.

MR. VADERS: Hi, Mark Vaders with Womble Bond Dickinson. Thank you for the presentation this morning, it was wonderful. A couple things came up in your presentation that bothered me a little bit, I think bothered some of the other people in this room a little bit, and have been for a while.

And that's in the course of your presentation you referred to the Cochrane reviews, you pointed to multiple pieces of published literature on NRT study design, and encouraged the use of NRT as a comparator in some of these studies. What it really seems to look like is you are asking applicants to demonstrate that one e-cigarette is a better NRT than another e-cigarette.

So, I would like you to speak to that. And additionally, you talked about the NYTS data, and I realize you have that data, and lots of other wonderful data sets out there that speak to youth use of flavors, but that is not product specific evidence. And applicants have to go through extensive bridging to get from their products to any general evidence that's out there.

If they can do the opposite of bridging, and show that that general evidence does not apply to their specific product, what role if any, does that play in their need to show adult benefit? Thank you.

DR. ALEXANDRIDIS: I can speak to the first part a little bit, I think. Yeah, I don't want to insinuate that we need to compare to NRT

specifically. I think that it can be useful information, it can be scientifically stimulating to look at that as a question, but it is definitely not required, and we think that the literature on cessation trials and guidance on NRT development can be useful as a starting point, or a jumping off point.

But yeah, we don't want to imply that NRT is the baseline, right? That's not what we're looking for in our review. And Ben, I think you can speak to the NYTS information.

DR. APELBERG: Yeah, definitely. First, just to piggy back on that, as we've talked about, our evaluation is about risks and benefits. And if an applicant is articulating the benefit to be smokers switching to the product in a way that it's going to reduce their risk, then we want to be able to have evidence to be confident that that's likely to happen.

So, I mean, I think that's the sort of framework that we're looking at. With respect to youth, and some of this is laid out in one of the sample MDOs that we have up on our website, and we've evaluated the evidence, and our conclusion is really that flavors are a big driver of youth use of ENDS

products, of e-cigarettes.

And we recognize that there are variations over time and particular brands that are popular, or particular device types, but we've also seen migration from one type of device to another as, for example, our enforcement priorities focused on a particular type. So, that's really the reason why we've framed this approach in this way.

Sort of recognizing that there's this inherent risk with respect to the appeal of these products. But looking for strong, robust, and reliable evidence of benefit to be able to overcome those risks. And so, as the risks to youth increase, the sort of magnitude and robustness of what we're looking for for benefit increases as well.

CDR. RUSSELL: Thank you for your response. I will now read a question from the virtual audience. In your hypothetical design, only a high comparator was included in the study design. Can you comment on whether both a high and low comparator are required for all abuse liability studies? If low comparators are not required, please explain why.

DR. SHROEDER: Yeah, so the low abuse

liability comparator product is not a requirement. It is a methodological decision that the applicant should consider when you're putting your package together. Again, as I think Ben plugged earlier, having a meeting request with FDA is often really helpful.

We've had some really helpful face to face, and just written responses with applicants where they've kind of brought up a hypothetical study design, and we've talked to them about pros and cons of different methodological decisions. We've brought up things that they may not have considered when designing their studies, and that could be one of those considerations to include in a meeting request.

CDR. RUSSELL: Thank you. The next question is from the virtual audience. Earlier today FDA recommended using two different regimens for HPHC testing. If an applicant has topography data from the ad-lib phase of an abuse liability study, can a single regimen based on the topography data be used in place of HCI and ICO regimens?

DR. SHROEDER: So, I think they want to use data from a human study to talk about the HPHC, to cover HPHC there?

CDR. RUSSELL: Yes.

DR. SHROEDER: I think we would need tox up here to answer that question. So, we may want to punt that to the panel seven when tox can address that.

CDR. RUSSELL: Thank you. This question will be posted to our panel seven for tox review. Our second question as well. For longer duration RCTs and cohort studies, there was mention of considering a max allowable number of CC consumed during the transitional periods of another product. Is there any guidance around what the max might look like?

DR. ALEXANDRIDIS: So, we don't have any strict guidance on that. But again, like I was saying earlier, you can look to the literature on development of smoking cessation trials to look at non-abstinent end points that have been used frequently in the literature, and I think the literature is replete with many examples on that. And yeah, that's probably a good starting point, and yeah, I just want to reiterate, thank you for the question, to note that that's, I think, a key consideration.

CDR. RUSSELL: We will now have questions

from the audience.

MS. ZDINAK: Hi, I have two more points. Could you talk a little bit more about the bridging strategy of multiple flavors if you are to randomly assign them to a single condition? I know earlier in abuse liability you talked about a specific topography method or measurement for bridging. So, if you have a blueberry you could bridge to a watermelon, I think was the example.

But that sounds like you actually have a machine and method to do that. But in behavioral studies we don't really have that. So, can you talk about how we can bridge that? And then the second point is with the flavors, and knowing that youth typically have oriented towards flavors, if they are removed from the market, how do we know then that youth just aren't going to go to the tobacco flavors, and then ENDS products?

And then what would you all do then if now they're all of a sudden they're using the tobacco flavored ENDS, and if then those go off market, what if they're back to cigarettes? So, that's a really complex situation there, how do you all deal with

that?

DR. APELBERG: Yeah, I can start with the second question. I think, like I said, our approach to this issue has really been driven by the evidence that we've compiled over the years, and over our experience, and it's really focused on the unique appeal -- well, one, the popularity of ENDS products with kids, and the particular appeal of non-tobacco flavored products.

I think we're always obviously continuing to evaluate the literature, as Apostolos talked about, both on the youth risk side, but also on the adult benefit side. So, I think we would just evaluate that, and communicate with you all if something substantive changed. But we feel like this is really a framework that aligns the risks with the benefits.

And like I talked about, to the extent that the risks are higher, we're really just looking for clear, or strong evidence of benefit to overcome that. I mean, the first question was about bridging specifically in the context of trials, do you want to talk about that?

DR. ALEXANDRIDIS: It's a very good point,

and well taken. I think that what we're trying to accomplish is the greatest level of specificity for a product or set of products that we can. And so, very clearly, yeah, randomizing people to a specific flavor is going to address that more concretely. But we understand the realities of at some level you're going to need to acknowledge that not everybody is going to find the same products, same flavors are the most appealing for them, right?

So, to that end, creating a flavored condition where people have that self-selection that is a pressure release there, and you can end up in a situation, for example, say where there is an unpopular flavor that does not get self-selected in that arm, and then you have to rely on other information available in the trial, but yet that is one clear consequence.

DR. APELBERG: Yeah, I'll just actually add onto that. In the context of a clinical study of behavior, if you're trying to bridge maybe from one fruit flavor to another, it might be useful to, if there is for example, pharmacokinetic data, topography data that kind of links those different flavors really

closely, intentions to use.

I mean that kind of additional information to sort of make the strongest case possible, that's where the experience you see with one flavor is reasonably expected to be replicated with another.

CDR. RUSSELL: Do we have another question from the audience? Come on down.

MS. SEIFERT: Hello everyone, can you hear me? Hi. My name is Jessica Seifert, I'm with PMI, and I wanted to -- I'm going to move this a little bit because I'm short. I believe a gentleman earlier had brought up the use of an RCT in order to demonstrate the added benefit of flavor over tobacco, and I just wanted a little bit of clarity.

Because scientifically RCTs are like the gold standard. However, when we're thinking about the outcome that we're looking for, which is demonstrating that the product has a benefit in the market, would you -- it seems to me that it would be more appropriate to do cohort studies or an actual use study over an RCT in order to appropriately demonstrate or be closer to what the marketplace would look like. Because folks can select, and be able to

actually see how they use the product.

DR. ALEXANDRIDIS: So, I understand, and I think agree, that as we get into the real world, we have more real world evidence, right? I think though, that at the end of the day, we understand that it's a pre-market pathway, and to make the comparison to drug development, we wouldn't expect post market data in a pre-market application.

And so that holds here as well. We do believe in the power, like you say, of actual use studies in a real world setting with a provision product to give us important insights, and be very useful. But we also acknowledge that it may not be necessary because a randomized control trial can give us enough to understand a product and characterize it in a pre-market context to make APPH considerations. Was there anything you wanted to add to that, Ben?

DR. APELBERG: Yeah, I'll just add, I mean it's sort of related to the question that came up earlier about the tradeoffs between a more controlled trial and more real world data. And part of that really does have to do with we're talking about products that were previously on the market, and

therefore you have that real world data.

I mean, I know alternatively there might be data from other countries where a product is marketed. But in that case we'd really want to be confident what the clear rationale is to why the experience in another country is likely to be replicated if a product is marketed here, but it's a good point.

MS. SEIFERT: Thank you.

CDR. RUSSELL: Come on down, sir.

MR. FISHER: Since nobody else is asking, a question for you, Dr. Miller. There's lots and lots of PK data, have you guys looked at, or thought about modeling PK parameters as part of an abuse liability assessment? And do you have any advice, or guidance, or musings?

DR. SHROEDER: Are you suggesting that we conduct the study, or that if there is a --

MR. FISHER: No, I'm suggesting that should an applicant be so moved to do, how might you look at that?

DR. SHROEDER: Right. So, we have seen modeling in our pharmacology department, and we have

analyzed modeling data. It is, again, it's a consideration for the applicant. Is that modeling data strong enough, is it valid? Include the justification, and the scientific support to support the modeling data, and be specific with regard to your product, and it's something that we can consider.

Again, if you wanted to come in to talk about your proposed approach prior to submitting, that's something we're always open to.

MR. FISHER: Okay, thank you very much.

CDR. RUSSELL: We do have another question from the virtual audience. FDA recommends two phase abuse liability studies. What are FDA's recommendations for the length of the ad-lib phase? And can ad-lib use testing be performed after a short period of non-use after the defined puffing phase, for example, on the same day?

DR. SHROEDER: Thank you for the question. In general we don't have prescribed or kind of guidelines about the duration of the ad-lib portion, or the duration between the prescribed use and the ad-lib portion of an abuse liability study. There are several considerations to think about when you're

designing that study. You'd like a sufficient time for wash out between the prescribed use, and the ad-lib situations.

So, I would recommend at least an hour between those situations, and the longer an ad-lib session is, the more likely it is to be relevant to actual use behavior. But we don't have specific guidelines or recommendations for the durations of those.

CDR. RUSSELL: Thank you. Our next virtual question, if a device has access restrictions will there still be a requirement to show that the flavors in the application provide an added benefit to adult smokers over tobacco flavored products?

DR. APELBERG: This actually is similar to a question that was asked earlier. Just to reiterate that FDA does think that there are novel access technologies that could be effective to mitigate risk in a way that would not sort of require the same magnitude of benefit as we've been talking about here today. But that really is contingent on the clear evidence that the controls are effective, and can't readily be disabled or defeated.

So, like I said earlier, we're happy to engage if potential applicants want to come in and discuss those controls, and also the kinds of evidence that we'd be looking for in terms of benefit.

CDR. RUSSELL: So, I would like to reiterate that if by chance you do have questions about your specific product, FDA does have a method. Prior to your pre-market application that you can submit a meeting request to FDA in efforts to discuss your products, and to get FDA's feedback on the type of studies, and any additional information that you may be seeking in reference for an authorization of your particular product.

That meeting request can be used for all three market pathways as well. Do we have any additional questions from the audience? While we're waiting, I will read a question from the audience, and I'm going to paraphrase this question. So, looking at abuse liability studies, and the question more so is looking at the amount of change or the percentage of change, decrease, or increase that FDA would be looking for in efforts to receive an MDO or an NSE order.

So, basically they're looking for what would be the requirement within abuse liability, they wanted to know what is the percentage of change in increase or decrease of triggers that would trigger an MDO or an NSE order for a particular product? It's very product specific, and so if you want to provide a generalized answer.

DR. SHROEDER: I'm not quite sure what the intent of the question is. But if there are differences between a tested product and the new product in an abuse liability study or any other type of study, it's important to provide as much information that you can that's appropriate to bridge the two products together. We don't have any triggers or kind of thresholds of similarity that we require between bridged products and new products.

And then again, an NSE or an MDO order is not contingent upon the similarities between a bridged product and a new product, it's based on the totality of evidence presented in the PMTA.

CDR. RUSSELL: Thank you. Do we have any additional questions from the audience? So, we do have some additional virtual questions. Press

releases for MDOs often cite one of the reasons for marketing denials as an ENDS brand being one of the most common brands of youth e-cigarette reported usage. Using that 26.6 percent of youth -- with youth use of 26.6 percent within the past 30 days of the flavored ENDS users.

If the APPH determination is the benefit to adult smokers of an individual non-tobacco flavored product weighed up against the youth use of the entire brand, and or youth use of an entire non-tobacco flavored category? That's part one.

DR. APELBERG: No, the risks and benefits are evaluated for that specific product under review. It may be that for context we might cite data on the brand broadly from NYTS for example, but the evaluation is product specific.

CDR. RUSSELL: Part two, and after this, this will be our last question for the panel. If a menthol flavored product demonstrates greater efficacy in assisting adult smokers to switching compared to the flavored tobacco product, would this evidence be sufficient to outweigh NYTS' data on the risk of youth use on the brand in which the product cites youth use

or non-youth use of menthol as an entire flavored category?

DR. APELBERG: I don't think I sort of understand the total nuance of the question. But broadly, menthol, like other non-tobacco flavored ENDS, what we would be looking for is robust and reliable evidence of added benefit, which for example, could be demonstrated by increased efficacy. So, that would be strong evidence on the benefit side.

And we would be evaluating the risk, we'd be evaluating the abuse liability, the toxicity, the sort of all the other components of that evaluation to make an overall APPH determination. Thank you, thank you to our panelists. While we do have some additional questions, those questions will be placed for the session seven panel discussion.

And if we have additional time, they will be answered during that time. Thank you. We will now break for lunch. Reconvening at approximately 1:10, thank you.

(Whereupon, the above-entitled matter went off the record at 11:56 a.m. and resumed at 1:15 p.m.)

CDR. RUSSELL: Good afternoon, we are

officially back from lunch, it is approximately 1:15. Welcome to those who are in person, and to those who are virtual. I am Commander Avena Russell, and I will be the moderator for the remaining of today. We're going to move directly into session six as it relates to FDA's toxicology review.

We'll start with Dr. Mamata De discussing hazard ID genetics toxicology assessments for PMTAs. Followed by Dr. Mary Irwin discussing considerations for assessing relative hazards, exposures, and risks for ENDS and other tobacco products. Dr. De?

DR. DE: Good afternoon, my name is Mamata De. I'm a senior reviewer in the Division of Nonclinical Science in the Office of Science. This presentation will focus on genotoxic hazard identification, and the challenges and limitations of hazard identification in pre-market tobacco product applications.

In today's presentation, I'll discuss the regulatory requirements for genotoxicity testing of new tobacco products submitted through the PMTA pathway. General topics covered today will include some specific issues and concerns encountered when

assessing different genotoxic assays during our review process, what we have learned about genotoxic hazard identification over the past several years, and I would also like to talk a little about our current thinking on genotoxicity assessment, and potential approaches moving forward.

For a new tobacco product to receive marketing authorization through the pre-market tobacco application pathway, FDA must determine that marketing the new tobacco product is appropriate for the protection of the public health.

When applicable, a comprehensive evaluation is performed on all new tobacco products to determine if there are toxicological concerns from all non-cancer and cancer hazards present in the product. As a part of this determination, tobacco products undergo an evolution of the genotoxic potential before a marketing order can be granted.

Genetic toxicity or genotoxicity is defined as damage to the DNA. DNA damage may cause mutations that have the potential to lead to cancer. Genotoxicants are defined as chemicals that induce adverse effects on genetic components within the cells

through a variety of mechanisms. These adverse effects may include mutation, aneuploidy, and clastogenicity.

The culmination of DNA damage is a critical initial step in the production of mutation following exposure to genotoxic constituents. Data in the literature indicate that 80 to 90 percent of carcinogens have a genotoxic mode of action, and a comprehensive analysis demonstrated that over 90 percent of recognized international agency for research on cancer group one chemical carcinogens are mutagenic.

Therefore, genotoxicity is a critical mechanism for carcinogenicity, and evaluating genotoxicity is an important part of CTP's review of new tobacco products. Now, when I say genotoxicity, we mean toxicity induced by a chemical that causes changes and mutations in DNA. These changes may include deletions, insertions, or alterations of a base pair in DNA found in the nucleus of a cell.

A chemical can also cause chromosomal damage or structure alteration of a chromosome. A mutagenic chemical has the potential to be a genotoxic

carcinogen. A battery of genotoxicity tests is therefore necessary to assess genotoxic potential of a given chemical. Which might be an ingredient, an additive, leachables, or paralyzing product found in the tobacco products.

Genotoxicity tests are conducted to detect chemicals that induce genetic damage through various mechanisms, thereby enabling hazard identification. So, why it is so important to assess genotoxic hazard from a regulatory perspective? Because once identified, genotoxic chemicals, which are potential carcinogens with a genotoxic mode of action can be factored into a subsequent cancer risk assessment.

There are several validated in vitro genotoxicity assays recommended for hazard identification. CTP's PMTA rule on guidance documents providing guidances on assessing the genotoxicity of tobacco products. The final rule of substantial equivalence and PMTA stress the need of genotoxicity hazard identification as part of comprehensive carcinogenic risk assessment for new tobacco products.

The ENDS PMTA guidance suggests using the international conference on harmonization S2R1

guidance for testing pharmaceuticals as a guide for genotoxicity testing. And the process of linking chemical to an adverse health outcome is known as hazard identification. The genotoxicity assessment of tobacco products poses several unique challenges.

For example, potential genotoxic chemicals in tobacco products can originate from direct addition of ingredients to the products, or the products itself, or through the degradation, combustion, and paralysis of these chemicals. Many harmful and potentially harmful concentrates commonly found in tobacco products are known genotoxicants, including acetaldehyde, formaldehyde, benzene, 1,3-butadiene, and so on.

Through our experience with toxicology review of PMTAs, CTP has also learned that ingredients and leachables from ENDS devices may also contribute to genotoxic and carcinogenic risk. Unlike HPHCs, the genotoxicity hazard of many of these ingredients are unknown, limited, or inconclusive. Thus, reliable genotoxicity assessments are critical for determining product safety.

The ICH S2R1 guidance is referenced in

CTP's revised PMTA ENDS guidance. The guidance was developed primarily to evaluate the genotoxicity of individual chemicals, most commonly, small molecules encountered in pharmaceuticals. The guidance describes the common features of standard genotoxicity test battery, and defines the standard battery of genotoxicity testing and data interpretation.

The ICH S2R1 guidance mentions assessment of mutagenicity in a bacterial reverse mutation assay. The test has been shown to detect relevant genetic changes, and the majority of genotoxins are rodent and human carcinogens. The guidance also mentions that genotoxicity should also be evaluated in mammalian cells in vitro, and or in vivo.

The ICH S2R1 guidelines may be informative when assessing potential genotoxic components. However, it is important to note that this guidance were developed primarily to evaluate the genotoxicity of individual chemicals, not the complex mixtures that typically are used as test articles when testing tobacco products.

Importantly, ICH S2 provides two options for the standard testing battery. As mentioned

earlier, the ENDS PMTA guidance suggests using ICH S2R1, which provides two options for the standard genotoxicity testing battery. In option one, a compound is testing using an in vitro mutagenicity analysis, an in vitro clastogenicity analysis, and in vivo test for assessing chromosomal damage in rodents.

Alternatively, the compound can be tested using an in vitro mutagenicity assay, and two in vivo assays as described in option two. In keeping with the tox 21 initiative to decrease animal use in scientific and regulatory research, CTP suggests that supportive in vitro assays with clear positive and negative data may be sufficient for hazard identification.

The ICH S2R1 guidance also provides support for the in vitro only testing when toxico or pharmacokinetic data indicates a compound is not systematically absorbed. In such cases, evaluation of a test compound using in vitro test is sufficient to assess genotoxicity risk. Several in vitro assays are commonly used to assess genotoxicity.

The first assay I will discuss in detail today is the Ames assay. Mutagenicity assays are

recommended for both option one and option two for standard battery and ICH genotoxicity guidance. The Ames assay is a bacterial mutagenicity assay, and considered as a very reliable genotoxicity assay with a high positive predictivity for DNA reactive chemical carcinogens.

Studies have shown that approximately 70 to 90 percent of mutagenic chemicals are also carcinogenic. Since mutagenicity is a major predictor of carcinogenic risk, genotoxicity assays such as the Ames assay have the potential to determine whether tobacco concentrants should be included in a risk assessment. The Ames assay is thus a powerful tool for genotoxic hazard identification.

Current regulatory paradigms, ICH Organization for Economic Cooperation Development use the Ames assay as a tool for hazard identification. Data analysis methods described in current regulatory paradigm to not estimate genotoxic or carcinogenic risk from Ames assay results. Several factors can affect Ames assay results, and the identification of potential hazards in tobacco products.

Some of these include statistical

selection, data interpretation, consideration selection, cytotoxicity, and so on. In addition to mutagenicity like the Ames test, ICH recommends genotoxicity assays that assess chromosomal damage, also known as clastogenicity. As part of this standard battery, ICH guidelines testing for chromosomal damage in mammalian cells using the in vitro chromosomal aberration assay, in vivo micronucleus assay, or in vitro mouse lymphoma time as gene mutation assay.

For reviewing clastogenicity of tobacco products, we have primarily received in vitro micronucleus assay data. Very few chromosomal aberration data were submitted, most likely due to known problems with excessive false positives. MLA assay tests for both mutagenicity and clastogenicity, but the assay is considerably more time consuming.

Test article selections poses similar challenges for both Ames and clastogenicity assays. Solvent selection and cell counting are additional difficulties for clastogenicity assessment in mammalian cells. Several issues are identified in vitro genotoxicity assays because of the solubility issues with the test articles.

Ethanol is used as a solvent, however, ethanol is a known cytotoxic chemical as per several peer reviewed publications. In addition, ethanol is also known to change metabolic enzyme activation induction or innervation of different seep enzymes. TK6 cells are known to have active P53 pathways that repair gene mutation. OECD guidelines mention to use the cells after three to four passages.

However, OECD rules are not always followed, and negative results even with known positive chemicals and mixtures are noted. For example, one out of six have referenced mixtures with known genotoxicants are found negative in the in vitro micronucleus assay using TK6 cells. Positive controls are found positive indicating the assay is valid.

However, known genotoxic comparator products came out negative in such assays, questioning the validity of the positive control itself. For example, Jacob et al 2099 showed one out of six have condensate contents acetaldehyde, acetamide, et cetera, which are known genotoxicants.

If the known genotoxic comparators test negative, the result with test article condensate is

questionable. Positive controls may provide valid results, but if one out of six condensates produces negative results, is the assay truly working for the tobacco products? To continue with the challenges in reviewing genotoxicity studies, we have also identified metabolic activation systems as another potential concern.

For example, certain metabolic activation systems for tobacco product testing might not always be sufficient because some components of tobacco products, such as nitrosamines are seeped to E1 substrates. Also there are species differences for substrates such as acrylamide, et cetera in response to seep to E1.

As such, scientific judgement needs to be exercised in case by case basis for bioactivation. Cell counting (phonetic) is an additional problem for in vitro genotoxicity assays where consistent transparent data analysis for control, positive controls, and test articles are important consideration for genotoxic assessment and hazard identification.

For example, for the in vitro micronucleus

assay, OECD recommends counting at least 2000 cells. However, different federal agencies have their own guidance for the number of cells that need to be counted. Under the same experimental conditions, counting an equal number of cells for the test articles and the comparing negative and positive controls helps avoid potential bias and misuse of statistical power.

Another major challenge in tobacco product evaluating using genotoxicity assays is cytotoxicity. For example, one of the major constituents in tobacco products is nicotine, which is cytotoxic, which is a limiting factor for test article concentration selection. Potential genotoxicants that are present in low concentration mixtures can never be tested adequately in the mutagenicity test due to the cytotoxicity of nicotine.

Scientifically, it is not impossible to extrapolate the data from genotoxicity assays to correlate human exposure for assessing carcinogenicity. In the absence of such data, a link between different concentration of genotoxicants that are present in the test article in vitro and

carcinogenicity risk assessment in humans could not be possible.

Nicotine is addictive, consumers commonly use tobacco products for decades. The total exposure to a toxicant affects the incidence and severity of adverse effects. Consumers commonly use tobacco products for decades. The level of genotoxicants that are too low to produce positive results in a genotoxicity assay may still produce genotoxic effects in humans when exposed over a lifetime.

Therefore, identification of hazard from test article mixtures is inherently complicated. By forming a toxicological evolution, specifically genotoxicity assessment on a chemical mixture such as e-liquid, aerosol, or aerosol condensate is multifaceted, and associated with challenges that may impair a total evaluation of tobacco products.

Moreover, we know e-liquids contain known genotoxicants, including HPHCs, these may be form added with ingredients or chemicals leeching into e-liquids from the device. While testing whole liquids may provide additional information about the genotoxicity of individual components in the product,

other factors may limit our confidence in drawing reliable conclusions from whole mixture analysis.

Genotoxicants formed during aerosolization may mask other potential genotoxic e-liquid components. Section 910(b)(1)(B) of the Food Drug and Cosmetics Act requires PMTA for a new product to contain a full statement of the components, ingredients, additives, and properties of such tobacco products. As such, CTP may consider tobacco products, that is Ames, e-liquids, and in aerosol to be a known intentional mixture.

OECD guidance clearly states that evaluation of mixtures may be better served using component based approach. Guidance from the European Food Safety Authority and World Health Organization recommends applying a component based approach for regulated products that contain fully defined or characterized mixtures.

These documents also provide guidance for products in which all compounds or concentrates of the mixtures are not required to be known, and for products with mixtures that have uncharacterized components. In this component based approach, the

constituent ingredients or chemicals contained in the mixture are assessed individually for their potential genotoxicity.

Because the guidance from EFSA and WHO are developed to address genotoxicants in mixtures of ingredients or flavoring in formulations for the food industry, if an applicant decides to use one or both of these approaches, they would need to be adapted to tobacco products with appropriate consideration for the route of exposures, or route of administration.

In 2023, FDA issued a revised guidance for PMTA in summation which recommends providing a full assessment of toxicological and pharmacological profile of a new tobacco product, which includes toxicologic data from literature, analysis of constituents, including HPHCs, and other toxicants. It also includes in vitro toxicologic studies such as genotoxicity studies and cytotoxicity studies, and computational bottling data.

In vivo toxicological studies, which are primarily used only to address unique toxicology issues that cannot be addressed by the alternative approaches can also be included. To extend to this

thought, data poor chemicals, that is chemicals with equivocal genotoxicity data are of concern.

Again, chemicals with no information, conflicting genotoxicity results, or studies with positive results or negative results that have methodological issues that prevent confident conclusions may be considered as data poor chemicals. So, in conclusion, genotoxicity and carcinogenicity relation of tobacco products requires a holistic approach for assessing cumulative toxicological risk.

Clear positive or negative data from the in vitro assays following relevant ICH S2R1 guidance may sufficient for hazard identification without the need of in vivo studies. A component based approach to hazard ID may be more informative for tobacco products due to unique issues, specifically associated with genotoxicity testing of whole aerosols and condensates. Thank you all, thank you for listening.

DR. IRWIN: Okay. Good afternoon, my name is Dr. Mary Irwin, and unfortunately my colleague, Dr. Jon Fallica cannot be here today due to a personal matter. So, I am a supervisory pharmacologist in the Center for Tobacco Products Division of non-Clinical

Science, and today I will be speaking to you about considerations in assessing relative hazards, exposures, and risks between electronic nicotine delivery system, or ENDS, and other tobacco products.

To give a brief overview of our agenda, we will discuss and consider components of risk assessment, including problem formulation, hazard identification, hazard assessment, and exposure assessment. And then we will combine these together and discuss the topics, and how they relate to risk assessment regarding carcinogens, non-carcinogens, and chemicals with very little empirical data.

Regarding the overarching regulatory context for such considerations in tobacco product assessments, there are a few important notes to make. In brief, a diverse array of risk related information on ingredients, leachables, and HPHCs is submitted to FDA by tobacco product applicants via the pre-market tobacco product application, or PMTA pathway.

But why? Under section 1114.7(K)(1)(I)(B) of the Code of Federal Regulations, a PMTA must contain all investigations published or known to, or which should be reasonably known to the applicant

regarding the toxicological profile of the new tobacco product related to the route of administration including but not limited to the genotoxicity, carcinogenicity, respiratory toxicity, cardiac toxicity, reproductive and developmental toxicity, and chronic repeat dose toxicity of the new tobacco product relative to other tobacco products.

The submitted risk related information often fit under specific and well accepted risk assessment categories that are geared towards chemical identification and the linkage of dose to outcome. Such as hazard identification, in which there is specific linkage of an ingredient, leachable, or HPHC with an adverse health outcome.

Hazard assessment, in which there is a weighing of evidence or expert judgment regarding the degree and nature of an ingredient's, leachable's, or HPHC's adverse effect. Exposure assessment, where there is an accounting of how much of a given ingredient, leachable, or HPHC a user may encounter during product use, how often the exposure occurs, and for how long the exposure occurs during product use, as well as over a lifetime.

And finally, risk assessment, in which all available information is combined, or not, if information is lacking, to estimate lifetime or changes in lifetime cancer and non-cancer risks. Put simply, tobacco products are mixtures of tobacco and chemicals such as ingredients, HPHCs, and leachables. Tobacco products are mixtures before product use, and there are mixtures during products.

For tobacco products that can be inhaled, additional factors like heat and airflow can impact the overall mixture during aerosolization or combustion. Thus, risk assessments for tobacco products require an evaluation of mixtures, and the methods for assessing mixtures are important in tobacco product evaluation.

So, are there established risk assessment guidelines? The short answer is yes. However, existing guidelines were not made for tobacco products, and in general do not detail how to perform comparative tobacco product assessments.

None the less, regulatory documents, such as the Environmental Protection Agency, or EPA's Risk Assessment Guidance for Superfund Part F, EPA's

inhalation dosimetry, and EPA's guidelines for carcinogen risk assessment together provide a structure that is commonly used to screen for toxicity issues.

In addition, the National Research Council formalized these key steps in risk assessment and eloquently detailed ways one can identify and account for uncertainty at every level of a given chemical's assessment. Together, these well cited documents provide a basis for screening chemicals or a mixture of chemicals, but were not developed specifically for comparing mixtures.

They also provide information regarding weight of evidence considerations such as certainty or uncertainty, but given the foundational context of these documents is different than that that's encountered in regulatory tobacco applications, there is space for expert judgment and follow up to impact the application of such architecture.

Generally, the steps of problem formulation, hazard ID, hazard assessment, and exposure assessment are important for overall risk assessment. For problem formulation, we may ask

questions such as what chemicals should be included in an assessment. For hazard ID, we ask are there any chemicals associated with averse health outcomes?

In hazard assessment, we may ask are the identified hazards of concern? What is the weight of evidence, or WOE for the hazard end point? For exposure assessment, we look at how much of a given chemical one is actually exposed to, and what chemicals are there of concern.

And then all of these come together to create a risk assessment where we ask does the combination of hazard and exposure information indicate that a user is likely to experience adverse health based on existing regulatory data, such as referenced toxicity data. The first step I will discuss with you is problem formulation.

The first question in problem formulation may be which products ingredients or constituents should be analyzed? This may be harmful in potentially harmful constituents, or HPHCs like those on our HPHC list, as well as ingredients added to the products. Then another question for problem formulation may be are any of these constituents

associated with adverse outcomes?

Further questions may get to the heart of mixture effects, or acute versus long term toxicities. Generally, as I mentioned, risk assessment combines information about the specific constituents, or combination of these constituents, and the level of exposure to form a decision about a tobacco product.

Additional considerations for the risk analysis generally may include what chemicals are in the aerosol, are there known health consequences related to the inhalation of the chemicals, and what is the level of exposure to the user? How about for the non-user, like second hand exposure? The general priority, again, for toxicology reviewers is to relate the dose of a given chemical to the adverse health outcome based on data.

After problem formulation we move forward in the risk evaluation process to hazard identification and assessment. The weight of evidence that a given constituent is hazardous to human health is the next step in the risk evaluation process. In general, agencies such as EPA provide a detailed accounting of all data points and or models that

factored into the final hazard identification, and have a consistent platform for adverse health endpoint verification and subsequent extrapolation.

One way that agencies like these operationalize a weight of evidence hierarchy is to account for all available data, such as epidemiological data, animal data, or mode of action information, and communicate the certainty regarding the weight of evidence through a tiering mechanism, such as the one shown here from EPA and IARC.

While there are a number of methodologies for assessing the weight of evidence for hazard identification, there are also a number of considerations for CTP in making a determination regarding toxicological hazard.

For example, while other agencies, such as FDA's Center for Food Safety and Applied Nutrition, now known as the Human Foods Program, the EPA, the European Food Safety Authority, or EFSA, the Joint FAO and World Health Organization Expert Committee on Food Additives, or JECFA, and the European Chemical Agency, or ECA, may have determined that a particular constituent is not genotoxic or carcinogenic.

It is imperative that CTP makes its own weight of evidence determination based on the unique exposure scenarios posed by tobacco products. Some of these agencies publish information on exposure to flavoring compounds, like those found in ENDS, via the oral route, or in the context of a food additive.

This analysis typically includes per capita intake across populations, as well as acceptable daily intakes. These evaluations are carefully considered by CTP, but we recognize that they rely on exposure assumptions that are different from inhaled products such as ENDS. Further, a finding of generally recognized as safe, or graphs for food products is determined based on oral consumption.

And the designation does not apply to the use or consumption of inhalable tobacco products, or to the individual ingredients and constituents included with tobacco products. One specific question that arises, considering a chemical's supporting information in tobacco product applications is when does route of exposure matter for hazard identification purposes?

For carcinogenicity studies, the route of

exposure can be extremely important. This is, in part, due to differences in metabolism between the lung and oral routes of exposure. After oral exposure, first pass metabolism occurs in the liver, which may detoxify chemicals. And if that metabolism pathway is not active in the lungs, one would expect different effects if inhalation exposure occurs.

Similarly, independent of route, lung specific metabolism is possible, which may create carcinogenic metabolites, like in the case of the tobacco specific nitrosamine, NNK. Conversely, it is possible that constituents of concern may not distribute well to important target organs, such as the lung when given orally. So, the portal of entry effects may ultimately be an importance consideration, particularly for reactive chemicals like aldehydes.

Of note, while carcinogenicity studies are generally dependent on the route of exposure, on the other hand, genotoxicity studies are route agnostic. Thus, inhalation may not be the most relevant route in such an assay, even if the product evaluated is intended to be inhaled. In vivo genotoxicity data would be uninterpretable if there is not evidence that

the test article reaches the tissue that is sampled.

Once the hazards are identified, the next step in the risk evaluation process is exposure assessment. That is how much of a given chemical would a user be exposed to? Within an exposure assessment, one can determine which constituents are of toxicological concern. A key part of that is determining to how much a user is exposed.

One can assess this by looking at how much is in the medium to which the users are exposed per hour, per day, or over a lifetime. Ultimately, in toxicology, the dose or quantity makes the poison. Here I am showing a classic view of exposure, which is typically the product of intensity of exposure, or how much is in the medium that comes in contact with a person.

Think exposure concentrations here, how much of a chemical is in a defined space, such as an inhalation volume for example? And then the frequency of exposure, or how often one is exposed during the day, and over a lifetime. And the duration of exposure, or how long one is exposed each time they use it during the day, or over a lifetime.

The EPA's 1992 guidelines on chemical exposure, and the National Academy of Science report recommend the 90th and 99th percentiles of exposure as default cut off values that can be considered health protective for chemical exposure evaluations. There are a few things to consider when looking at submitted exposure information.

First, a reviewer will look for the quantity and behavior assumptions provided by the applicant. This information is provided in a number of forms that may include micrograms per gram, micrograms per milliliter, micrograms per cartridge, and so on. However, in order to compare within and across product categories, the exposure units need to be converted to common units.

An applicant can provide information regarding the expected use patterns based on use per day, for example cartridges per day, or puffs per day. For exposure assessments in general, information regarding specific exposure route is most useful. For example, aerosol data for ENDS, or extraction data from smokeless tobacco products.

Once all the hazards have been identified

assessed, and exposure has been determined, the next step in the process is to move towards risk assessment. This step looks at the combination of hazard and exposure information to determine if a user is likely to experience adverse health based on the data.

Looking at tobacco products specifically it is evident that toxicological risk can come from many different sources depending on the tobacco product being considered. For example, due to high temperatures of burning, the toxicological risk from cigarettes is primarily due to pyrolysis products.

On the contrary, smokeless tobacco products do not burn, so the ingredients added for flavoring, and the HPHCs extracted from the product itself will have the biggest impact on toxicological risk. For ENDS devices, the temperatures that they achieve are often lower than cigarettes. And therefore, while pyrolysis products still appear, they may play less of a role in the potential toxicological risk as flavoring ingredients and leachable chemicals are transferred whole into the aerosol.

Thus, ingredients in leachables, as well

as pyrolysis products, such as HPHCs should be included in an evaluation of potential hazards that contribute to the toxicological risk of ENDS products. One example for consideration of toxicological risk would be the cancer risk of ENDS products. As I mentioned on the last slide, due to generally lower levels of heat, ENDS devices often have lower levels of listed HPHCs compared to cigarettes.

However, when the HPHC list was created, FDA's tobacco product authorities were limited to cigarettes, cigarette tobacco, roll your own tobacco, and smokeless tobacco products, and the list of HPHCs reflected known contributors of risk presented by those products. Many HPHCs pose carcinogenic risk to users, so some may assume that lower HPHCs mean these products necessarily have lower cancer risk.

Indeed, there remains a cancer risk for ENDS even if only HPHCs are considered. However, ENDS are electronic devices that might be made from heavy metals, plastics, and a liquid formulation with intentionally added ingredients or inadvertently introduced leachates. Thus, the overall cancer risk may be greater than that posed by HPHCs alone.

To understand potential cancer risk, cancer reference toxicity values, such as inhalation unit risks, or IURs link the exposure to the risk. Specifically an IUR provides a risk estimate based on exposure of 1 microgram per meter cubed for a given chemical over a lifetime of exposure. Due to a linear relationship in the dose response curve, an IUR can be used to link the lifetime of exposure to a potential lifetime cancer risk at any level of exposure.

Unfortunately there are only approximately 30 IURs available from sources such as EPA and CAL EPA. Thus, there is general consensus in the literature and among other sources that a threshold of toxicological concern, or TTC may be useful. A TTC is the level at which genotoxicity is of likely concern for chemicals that lack empirical data.

Due to the assumption of linearity that I mentioned earlier, a TTC for genotoxicity begins as a generic slope factor for cancer risk of data poor chemicals. Thus, it is possible to use a TTC as a cancer slope factor for chemicals that do not have an IUR. With potential reference values for cancer potency, specifically the IURs in TTC, we are able to

associate the dose that a user is exposed to to the potential cancer risk associated for an individual product.

And also compare between products using a calculation of excess lifetime cancer risk, or ELCR. Importantly, ELCR calculations are estimates of cancer risk, they do not specify the actual risk associated with a product. ELCRs have been used, especially when there are no long term epidemiological studies to quantify the actual risk of cancer in humans.

Another consideration is that the analysis of ELCR is dependent on the strength and number of assumptions, and the overall weight of evidence approach for hazard identification that we discussed earlier. To calculate a composite ELCR, a microgram per day exposure for a particular compound is divided by the adjusted IUR, adjusted for exposure duration, and a risk level.

Or a default cancer slope factor such as TTC value. Then the ELCRs as calculated for each genotoxic or carcinogenic compound are added together to get a composite ELCR, or ELCRC. There are a number of advantages to the use of ELCR for cancer risk

assessment. The use of ELCR allows estimates of numerical risk at all doses of exposure, and allows the comparison of potency between chemicals at a particular risk level.

However, there are disadvantages as well. The additive nature of the analysis ignores possible synergy or antagonism within the mixture of a tobacco product. And all sources of carcinogenic risk may not have been considered if there is incomplete hazard identification. Thus, ELCRs may be an over or under estimate of the actual risk.

The accuracy of this analysis may be increased by providing data to replace those assumptions that had to be made. For example, 100 percent exposure, a 52 year lifetime, 100 percent bioavailability, and the default cancer slope factor, and considering additional sources of carcinogenic risk.

Cancer risk is just one of the many toxicological risks that are concerning for tobacco products. Non-cancer hazards associated with tobacco products have been recognized for many years, including respiratory toxicity risks for inhaled

products, cardiovascular risks, and other toxicological risks, such as organ specific toxicities, and reproductive and developmental toxicities.

These risks are part of the overall health risk of a tobacco product. Importantly, unlike cancer reference toxicity values, the toxicity values associated with non-cancer hazards do not have an assumption of linearity. That is to say they do not provide information regarding the severity of a response above the established level.

The level therefore links exposure and response giving a level below which no adverse effect is expected, but cannot be extrapolated easily according to increasing dose. Toxicity values for non-cancer hazard result in a calculation of hazard quotient, where the exposure to the hazard is divided by the referenced concentration.

A ratio then of one indicates that the exposure of concern is at the reference value. Whereas above one would indicate that the exposure is greater than the reference value. For non-cancer assessment, there are some considerations to keep in

mind.

While concerns can be identified across products in product categories, and risks can be estimated at multiple doses, and chemicals that have similar adverse health endpoints can be potentially compared, due to no assumption of linearity, one cannot necessarily determine how much higher the risk is when an ingredient is measured at a higher level than the reference concentration.

And the relative risk between comparator products may be difficult to understand when one or both levels exceed the reference concentration. All in all, when considering toxicological risk assessment of tobacco products, one must walk through each step of the risk evaluation process to ensure that there is correct problem formulation, accurate hazard identification and assessment, and defined exposure amounts.

So that the risk may be evaluated across the individual product, and then compared according to the Tobacco Control Act. To summarize, there are a number of considerations to keep in mind when looking at the risk assessment of tobacco products. CTP will

consider all potential sources of toxicological risk, which may vary based on product.

Inhalation products, an oral products differ in their weight of evidence for hazard identification due to the route of administration and exposure context. For exposure context, for example, potential interactions may occur between e-liquid constituents and metals from ENDS that ultimately may affect the lung.

Further, combusted products, heated products, and non-heated products like smokeless tobacco products may all have different drivers of potential risk due to the nature of the combustion and pyrolysis processes. Other considerations to keep in mind include both EPA and NAS suggest that exposure should be calculated at the 90th percentile of use.

Additionally, this may be an established level, like 20 cigarettes per day, or more variable due to differences in technology like for ENDS. While CTP has not yet established or adopted a particular TTC value at this time for cancer or non-cancer hazards, a TTC based approach is reasonable when empirical data is lacking.

Further, non-cancer hazard quotient calculations have no assumption of linearity. And therefore, potency above the referenced concentration cannot be extrapolated. And due to that lack of linearity, one cannot necessarily determine how much higher the risk is when an ingredient is measured at a higher level.

I would like to thank you for your attention today, and if you have any questions you can ask during the panel, or email askctp. Thank you.

CDR. RUSSELL: Okay, this concludes our presentation portion of our open public meeting. We will begin with session six panel Q&A period. Just a gentle reminder to please keep your questions related to the presentation that was presented only during session six. And if the panelists could come up and take their seats? I will read a few bios while they are getting adjusted.

I'll start with Dr. Mary Irwin. Dr. Irwin serves as a supervisory pharmacologist in the Division of non-Clinical Science within the Office of Science since 2021. She joined CTP in 2016 as a toxicologist. Currently Dr. Irwin supervises and mentors a team of

toxicology reviewers who work on all aspects of tobacco product regulation.

She provides scientific training on toxicology and risk assessment topics to her division. Before joining CTP, Dr. Irwin worked in academia, including a decade of cancer research, her experience spanning her PhD and post doctorate work at Karmanos Cancer Institute and Dr. Anderson Cancer Center. Welcome back, Dr. Irwin.

Dr. Chad Brocker. Dr. Brocker serves as a supervisory toxicologist in the Division of non-Clinical Science in the Office of Science since 2022. Dr. Brocker joined CTP in 2018 as a toxicology reviewer. He is a diplomat of the American Board of Toxicology, he holds a bachelor's in biochemistry from Colorado College, and a PhD in toxicology from the University of Colorado.

Prior to joining CTP, he trained as a post-doctoral fellow at the National Cancer Institute. Welcome, Dr. Brocker. Dr. Luis Valerio, Jr. Dr. Valerio is an associate director of the Division of non-Clinical Science in the Office of Science. Dr. Valerio has over 20 years of regulatory toxicology

experience at FDA, including at the Center for Food Safety and Applied Nutrition, the Center for Drug Evaluation and Research, and CTP.

His experience also stems from industry, safety of topical applied consumer products, and food flavor science and manufacturing. Dr. Valerio is a board certified toxicologist, he performed his post-doctoral in gastrointerology at the University of Colorado School of Medicine. He holds a PhD in pharmaceutical science from the University of Colorado. Welcome, Dr. Valerio.

And last, but not least, Dr. Hans Rosenfeldt. Dr. Rosenfeldt is a director of the Division of non-Clinical Science in the Office of Science. In his current role, Dr. Rosenfeldt supervises and mentors a deputy director and associate director, and mentors the Division of non-Clinical Science leadership team, which in turn he oversees the work of toxicologists and environmental scientists who work on all aspects of tobacco product regulation.

Dr. Rosenfeldt has conducted technical project lead reviews for the PMTA program, secondary reviews for the SE and MRTPA program, and has mentored

division staff working on regulatory reviews at all levels. Dr. Rosenfeldt joined CTP in 2012 as a toxicology reviewer, and has served in the roles of branch chief, deputy division director, and lastly, division director in 2021.

Prior to joining CTP, Dr. Rosenfeldt worked for six years as a pharmacology toxicology reviewer of inhaled drugs, cancer drugs, and drugs indicated for rheumatoid conditions in the Office of New Drugs at the Center of Drug Evaluation and Research. Prior to joining FDA Dr. Rosenfeldt conducted post-doctoral work in the areas of cancer biology with a focus on oropharyngeal cancer, and signal transduction.

Dr. Rosenfeldt holds a PhD from the School of Biomedical Sciences at the University of Texas Southwestern Medical. Welcome, Dr. Rosenfeldt. We will now begin with our first question from the audience. We will do the same, as we will do a two to two ratio, or two questions from the audience, and two questions from our virtual audience. Do we have any questions from the audience at this time? Come on up, sir.

MR. SOLYST: Hello, my name is Jim Solyst, I'm a consultant with my own firm, and I have industry clients. Dr. Irwin, it was sort of reassuring to see your reference to EPA, and National Academy of Sciences recommendations, guidance on toxicological risk assessment. I was wondering how far that approach extends to other issues that you face.

One that comes to mind is simply defining or interpreting what APPH means, and whether or not guidance or experiences you could gather from EPA and National Academy committees would be a benefit to defining that very significant definition?

DR. IRWIN: So, I think the definition of APPH is a little bit bigger than just toxicology alone, thankfully. Dr. Rosenfeldt, or perhaps Todd Cecil, or Matthew might be better to answer that type of question. I can say we do look heavily at the risk assessment guidelines from the various other regulatory agencies to help guide.

And I think that's a great place to start for general risk assessment information. Thankfully, toxicology has a lot of background in that from many, many different regulatory agencies. But the question

of how that fits into APPH, and how we might learn from those other agencies for APPH would probably be best in panel seven.

CDR. RUSSELL: Thank you. Do we have any other questions from the audience?

MR. CHAUDHARY: Hi, I'm Nveed Chaudhary from Broughton Life Sciences. Your colleague presented earlier on about the fact that you're getting lots of applicants seeing negative 1R6F tests in the micronucleus assay. I'm not quite sure where we landed on that, is there a recommendation going forward from that observation?

DR. BROCKER: Sure. So Mamata, in her presentation, she laid out a number of specific concerns that we've noticed in terms of dosing is one thing with the test article, also cytotoxicity of both solvent and the test article. So, I think providing scientific rationale for the dosing that you are using in your assays is important.

And all of that, at least I know those concerns are explicitly laid out in some of the assay specific OECD guidance. So, I would recommend look to the guidance, look to ICH guidance, and specifically

the assay specific OECD guidance. It does provide some outlines how to address some of those concerns. And importantly, include that information in your submission, so I think that that is important.

DR. ROSENFELDT: But the larger point is that this is a positive control. And just like in any experiment, if the positive control doesn't work, there is some concern.

MR. CHAUDHARY: Well, I think we're seeing the situation where the positive control, the 1R6F is causing cytotoxicity at the levels used for dosing, but you're still not seeing any response in the genotoxicity assay. We've seen this with a number of different products. So, are we saying don't do the assay, is there a clear recommendation? I guess is what I'm asking.

DR. ROSENFELDT: So, I think that perhaps it would be best if you contacted us separately for a meeting.

MR. CHAUDHARY: Okay, thank you.

CDR. RUSSELL: Thank you. So, I have a two segment question here, and so they'll be read as two separate questions from the virtual audience, and

this is paraphrased, and shortened. From publicly available records, some ENDS applicants have submitted information from new animal toxicity studies while others have not, but their similar products have all been granted marketing others.

Other applicants conducted in vivo genotoxicity studies to address positive in vitro results. How does FDA intend to better communicate guidance to industry that in vivo toxicity studies generally need not be conducted except to answer questions that cannot be addressed by alternative approaches?

DR. VALERIO: Thanks. Thank you for the question. So, specifically, it's hard to say exactly. We really can't say what you need to do, because this is going to be a data dependent situation as to whether you would need the in vivo studies or not.

But, there is certainly CTP is part of the FDA's predictive toxicology roadmap where we advocate for use of alternative methods when appropriate.

So, whether the need for in vivo study is there or not, would basically be, you know, upon your decision whether to proceed with that.

You could alternatively approach us and ask us whether you think before undertaking, for example, a large study in vivo chronic study, that would probably be advisable. And then, we could provide you more specific guidance about your situation.

But, certainly there are times when an alternative method may not be able to predict the hazard, if you will, for the test article. And, it might be more important to look at an in vivo study, especially if the alternative method isn't able to model a chronic disease.

So, that's basically the difference.

CDR. RUSSELL: Thank you. The second portion of this question is, in response to FDA's comment that including a combustible cigarette comparison product in genotoxicity studies would have been needed, one applicant explained that a direct in vivo comparison is unnecessary where there are readily available comparison data to inform a more complete and relevant risk profile, as is true for combustible cigarettes.

Does FDA agree? And, will it communicate

to industry that comparisons to combustible cigarettes should be based on available information wherever possible, and whenever possible?

DR. ROSENFELDT: So, that was very complicated.

CDR. RUSSELL: Would you like --

DR. ROSENFELDT: Can we -- can we try it one more time?

CDR. RUSSELL: Sure. I can read that again.

In response to FDA's comment that including a combustible cigarette comparison product in genotoxicity studies would have been needed, one applicant explained that a direct in vivo comparison is unnecessary where there are readily available comparison data to inform a more complete and relevant risk profile, as is true for combustible cigarettes.

Does FDA agree? And, will it communicate to industry that comparisons to combustible cigarettes should be based on available information whenever and wherever possible?

DR. ROSENFELDT: I think the question is very complex. And, I think that in the end, I think I

would fall back on the PMTA rule and the guidance for that.

And, for specific situations, for stakeholders to contact the FDA on that. In general, one would need to look at the overall toxicological profile of the product, you know, as part of an application.

CDR. RUSSELL: Thank you. We will now take a question from our audience.

MR. FISHER: Hi guys, it's me again. I'm -- if you'll indulge me, I'm going to do two.

CDR. RUSSELL: Be our guest.

MR. FISHER: Thank you so much. So, in the genotoxicity discussion you guys went through the S2(R1) guidance. And, then seemed to back away from it and raised this mixture toxicology approach through EFSA.

So, it's kind of similar to the question this gentleman asked before. Are we doing S2(R1)? Or, are we doing EFSA for mixtures?

DR. VALERIO: Well, I think the component-based approach is another approach that's recommended by other regulatory agencies.

MR. FISHER: Mm-hmm.

DR. VALERIO: And, it's well defined. So, I think -- I think that could be an alternative to address that issue with the previous.

DR. ROSENFELDT: I would add that you know, for particular components, one could readily follow ICH S2(R1).

MR. FISHER: For particular components?

DR. ROSENFELDT: Yes.

MR. FISHER: You're talking about --

DR. ROSENFELDT: If you're taking a component-based approach, one could look at, use ICH.

MR. FISHER: But, not for the whole mixture?

DR. ROSENFELDT: That gets very complicated.

MR. FISHER: Okay. We'll leave that one. The second question, again, it was mentioned that a positive or negative finding in the in vitro and then assay might be sufficient without going to in vivo.

But, you know, if you're following S2(R1), one of the sequelae of a positive finding in the in vitro assay is in vivo studies to confirm that.

So, how would -- how would the agency evaluate in vivo data in light of a positive in vitro finding?

DR. ROSENFELDT: Right. So, ICH S2(R1) has a section in it, and I don't have the guidance in front of me, that discusses the conditions in which perhaps the in vivo approach creates -- is not as interpretable.

I'm paraphrasing. I don't have the language. We did have a quote from ICH in the presentation.

So, it gets complicated. But, I think the best scenario is, you know, if you have a specific situation, to come talk to us.

MR. FISHER: Okay. Thank you.

CDR. RUSSELL: I will take another question from the audience.

MS. BOOTH: Hi. I'm Kellsi Booth, Turning Point Brands. So, as you mentioned, there are many instances where the genotoxic hazard is limited, or we really don't know, kind of doing our best guess.

And, there's also little guidance on the comparative aspect of this assessment for tobacco

products. What sorts of tradeoffs do you take under consideration?

And, do you anticipate sharing any additional resources on this topic, like reviewer stats?

DR. ROSENFELDT: Could you clarify tradeoffs?

MS. BOOTH: Yeah. So, say for example there's an ingredient that could be of potential concern. It's a cancer risk, but, 99 percent reduction and all the other cancer risk, just that one thing.

DR. ROSENFELDT: So, maybe that's for the next section.

MS. BOOTH: Okay.

DR. ROSENFELDT: Because that goes to the question of APPH.

CDR. RUSSELL: Thank you. We have another question from the virtual audience. If genotoxicity studies are route agnostic, why is data generated to support food additives regarded as essentially unacceptable and not reviewed on a case by case basis as it relates to ENDS?

DR. IRWIN: So, I think I said it in the presentation. But, CTP will carefully evaluate all of the previous agencies, I listed a whole bunch of them, decisions on individual constituents and take their weight of evidence into account.

I think it becomes more problematic when you start looking at, for example, an oral carcinogenicity study versus an inhaled product. That's where CTP might have to think about how that factors into our determination for weight of evidence ultimately.

DR. ROSENFELDT: Can I? I would add too that -- that it's actually very complicated, in the sense that for example, the carcinogenicity study, you know, there are things that cancer specifically through inhalation, like formaldehyde and things that, you know, cause cancer through the oral route.

But, things are different when one is looking at a genotoxicity study. And, the reason is that in a genotoxicity study, there's a -- if it's in vivo, there's a specific sample tissue.

And, if the test article doesn't reach that sample tissue, for example, the bone marrow in

the micronucleus assay, if it doesn't get to the bone marrow, there's no test.

And so, -- so, that's why, you know, if one wants to test, for example, whether something is genotoxic in vivo and, you know, say having something come through in inhalation, you know, you do use the inhalation route.

But, that -- the test article doesn't get to the bone marrow through inhalation then you don't have the test.

In those situations, it might be more useful to use the oral route or IP or something like that, to get the test article to the bone marrow, because that is the tissue that's being sampled.

I hope that makes sense.

CDR. RUSSELL: Thank you. We have another question from the virtual audience. In the -- and, I'm going to paraphrase this just a little.

So, in the first toxicology presentation it was suggested that genotoxins formed during aerosolization that masks, may mask over other potential genotoxicity liquid components.

They're asking, can you provide an example

and illustrate how this hurdle could be overcome.

DR. BROCKER: Sure. So, there's quite a few HPHCs that are known genotoxicants. And, so as far as a way to get a, looking at that as a hurdle.

I think again, in the second part of the presentation where the component-based approach was discussed, provides a way to individually assess potential genotoxic concerns as maybe a, you know, one approach to address a situation such as that.

DR. ROSENFELDT: So, the issue might be, for example, if you have something that is positive in an assay and you have an unknown ingredient and mixed with a known positive, if something is positive in the assay, do you know if that is caused by the positive HP -- the HPHC you know is positive or the unknown ingredient.

And, I think that that's what we're trying to get to.

CDR. RUSSELL: Great. Thank you. Do we have any additional questions from the audience?

If not, this concludes our panel session for Section 6. And, we will take a quick 15 minute break. We will reconvene, how about at approximately

2:45.

(Whereupon, the above-entitled matter went off the record at 2:28 p.m. and resumed at 2:46 p.m.)

CDR. RUSSELL: I know you guys are ready to get started with Panel 7. And, while our panelists are taking their seats and getting situated, I will begin to introduce some of our panelists.

I think we have about nine of your guys with us today. And, I guess FDA saved the best for last.

So, just to reiterate, this is our live panel session where we provide you with the opportunity to ask anything within the scope of this meeting.

We will allow questions within the scope of the meeting, within the content of the presentations that you have heard within the past two days.

We ask that if you have product specific questions, that you save those product specific questions, and you can submit a meeting request so that you can meet with FDA and ask those questions specifically.

And first, I would like to introduce Dr. Michael Morschauser. Dr. Morschauser is a Supervisor Engineer in the Office of Science.

He has been with CTP for eight years starting as a primary reviewer. Prior to CTP he worked post-market surveillance for the Centers for Devices in Radiological Health.

He has a PhD in Biomedical Engineering from the University of Maryland. Welcome Dr. Morschauser.

Dr. Shannon Hanna. Dr. Hanna is a Supervisory Biologist in the Environmental Science Branch at CTP.

He has been with CTP for over seven years. Prior to joining the center, he was a researcher at the National Institute of Standards and Technology.

His expertise is in XO Toxicology of Novel Substances in the Environment. Dr. Hanna has a PhD in Environmental Science Management from UC Santa Barbara.

Dr. Bridget Ambrose. Dr. Ambrose is the Director of the Division of Population Health Science.

She joined CTP in 2011 as an Epidemiologist. She has served as an Epidemiology Reviewer for CTP's first PMTA and MRTPA applications.

She served as the Chief of Epidemiology Branch prior to assuming Division leadership. And, has served as a technical project lead on numerous PMTAs.

Dr. Ambrose has over 20 years of research experience in tobacco control and tobacco regulatory science. Her scientific expertise includes advanced training in longitudinal research methods.

Dr. Ambrose has -- was CTP's lead Epidemiologist involved in the design and implementation of the PAS study. She has published in top tier biomedical journals and has been twice recognized as highly cited researcher.

In her current role she oversees the research, regulatory, and product review efforts of nearly 70 scientists from the Social Science, Epidemiology, and Statistic disciplines.

Dr. Ambrose holds a PHD in Epidemiology from Johns Hopkins University, an MPH in Epidemiology and Biostatistics from George Washington University,

and a BA in Sociology and Anthropology from the College of Holy Cross. Welcome Dr. Ambrose.

Dr. Colleen Rogers. Dr. Rogers is the Director of the Division of Produce Science in the Office of Science.

Dr. Rogers has nearly 20 years of regulatory experience at FDA. Joining CTP in 2015, she worked in FDA Centers for Drug Evaluation and Research where she developed drug regulation and led a team that reviewed new drug applications.

In her current role, Dr. Rogers oversees the regulatory research and product review efforts of nearly 120 scientists from the chemistry, engineering, and microbiology disciplines who evaluate the composition, design, and stability of tobacco products.

Before joining FDA, Dr. Rogers completed a post-Doctoral Fellowship at the University Services University.

She holds a PhD in Medical Microbiology and Immunology from the University of Wisconsin-Madison, and a BS in Microbiology from the University of Illinois. Welcome Dr. Rogers.

Dr. Lynn Hull. Dr. Hull is the Deputy Director of the Division of Individual Health Science.

She joined CTP in 2014 as a Behavioral and Clinical Pharmacology Reviewer. In her current role she is responsible for the oversight of the Division of Individual Health Science, which she is involved in regulatory research and product review efforts from the medical, behavioral, and clinical pharmacology disciplines.

Prior to her work at FDA, Dr. Hull was an AAA Science and Technology Fellow at NCI and has completed her graduate work in pharmacology and toxicology at Virginia Commonwealth University. Welcome Dr. Hull.

In addition, I would like to bring back our esteemed panelists, Drs. Apelberg, Cecil, Rosenfeldt, Cristi, and Dr. Matthew Farrelly.

With that, we will begin our first question for Panel Seven. It will be the same or similar. However, due to us having a large audience here, we would like to give the audience as much opportunity to ask the panel any questions that they may have in reference to the presentations.

We will start with them face to face first. And then we will rotate face to face to virtual questions.

Dr. Farrelly will start first. He's going to ask one of the first questions. And, this is from our virtual questions.

DR. FARRELLY: Is this thing working? There we go. This is about APPH and it's come up online.

It's come up the last couple of days. So, I thought I would just tackle that one head on since we've received a number of related questions about how we weigh all the different factors that feed into APPH.

And, you know, our goal is to become increasingly transparent about our decision making framework as it relates to APPH. But, as you've seen from the presentations about toxicology, of course, about the benefits side and the studies quantifying the benefits, that it's never going to be a simple formula.

It's not like, you know, you can easily predict in advance what will come out as APPH. So,

our goal, like I said, has become increasingly transparent about how we're going about that decision making.

But, I think some seem to hope or expect that it will be, you know, some kind of formula that's used so we can plug in some inputs and out comes APPH.

And, I don't think we'll ever get there, because of just the complexity inherent in tobacco products, in the risk assessment, and even the benefits' assessment.

So, I wanted to hit that one head on, fairly on. And, it's true, the other thing that comes up related to this is how do we factor in the information that's provided in the applications as well as the broader studies?

You know, some studies that say, well ENDS are effective in getting smokers to switch. Or, you know, the studies that we talk about with youth appeal and flavors.

We're constantly reviewing that literature. And, we do factor that in as we look at application data. But, that's really where we focus.

We have to start with all the information

that applicants submit with their studies as the starting point. And then, of course, you know, that context about youth use and the appeal of flavors.

And then, other studies that are informing our decisions about APPH, we're always looking at that. So, it's a combination of both of those things.

And so, I know that may not be the answer that you all want. But, that's just the way that the complexity of the product demands of us.

So, and I welcome any of you to answer that. But, I wanted to hit that one right away.

CDR. RUSSELL: And, just so that you guys are aware, I'll go ahead and read that question so that you kind of have the framework for Dr. Farrelly's response.

FDA -- we have received a number of questions on the topic of what factors -- what factors FDA considers in making its APPH determination.

These questions include broad topics such as how do we operationalize an APPH standard and integrate all the various factors and data sources to reach a holistic decision in how FDA evaluates a continuum of risk upon reduction products like e-

cigarettes in the PMTA process.

We also have received numerous questions on how FDA factors in the lower negative health rate -- health effects of vaping and the use of vaping by smokers to quit smoking, into its APPH analysis. And, that was the kind of framework for Dr. Farrelly's response.

We would now like to bring questions from our live audience, face to face, if anyone has any questions?

Well, the virtual audience does.

(Laughter.)

CDR. RUSSELL: There have been a few times, yesterday and today, that FDA has directed the question to reach out to FDA with the specific question related to testing.

But, in my experience, FDA had not been willing or able to provide applications specific feedback like this in the review process. And, have suggested it for the applicant to determine on their own.

Is FDA going to provide more specific directions moving forward?

DR. STARK: I'll start and let others jump in. And, I'm going to borrow a note from Rosa yesterday and say, yes.

And then, I'll be a little bit more verbose, which I usually am. And add, the fact that in the past we haven't been as open and engaging because the standard really has been for the applicant to provide that.

Moving forward, our goal is to be transparent with our decision making, discuss some of the science and how it's changing and how that factors into our determinations for each of our premarket programs, as well as any other new factors to consider.

We can provide generalities for each of the specific disciplines that we have. But, at the end of the day, it will be product specific. So, we will have to look at those cases in each application.

At a public forum or posting online, we can't necessarily do that. And, that's where you're seeing requests to have a meeting with us or discuss those circumstances.

We'll also do our best if there are

deficiency letters or other communications to provide additional opportunities for clarification in that process so that folks are more prepared to respond to those letters as well as plan for future submissions.

DR. CECIL: Good. And, I'll jump on top of that and say that when we talk about coming in and talking to us about an application, we're talking about phase zero, before you actually sent in an application to us.

It makes a lot more sense to talk to you about your applications before you spend all the time and money doing the testing and identifying finding CROs to do the work for you.

When we are looking at these, keep in mind, we don't have all of the information you have about your product. So, the answers you're likely to get are, that seems reasonable.

But, we can't actually say, yes. That's exactly what we want. Besides, we probably wouldn't say that because that also depends upon the quality of the information we get and the specific information that comes in in that application.

However, if you want to discuss approaches

and you want to talk about those sorts of things, it's best to do that at phase zero before you ever apply.

Once we've actually started the application process and reviewing your application, at that point it's difficult for us to have meetings with you about those products.

And, in fact, we aren't -- we're not allowed to have discussions with you at that -- about those products. So, if we have an opportunity early on is the best.

As Cristi pointed out, after we have a deficiency letter, if the deficiencies are unclear, you can certainly send back a request for clarification. And, we can help in clarifying any of the deficiencies that are there so that you understand what it is that we're trying to get at in those deficiencies.

CDR. RUSSELL: Thank you. I have another question from the virtual audience. Many age-gating technologies require age activation every few days amongst other active interventions and these can be -- I'm going to skip over that. Yes, I could not read that. There might also be -- there might be a

technology barrier for some populations. The sum effect of the age-gating technologies can become a significant barrier to switching from cigarettes. How is the agency going to balance the justifiable concern about youth initiation with the equally important potential benefit in adult smokers?

DR. APELBERG: Yes, I mean, I think those are all fair points when we talk about device access controls. I think there's a lot to learn about the implications, how they can be used, how effective they might be, what impact it would have, not just on those who are trying to stop from using, but those who could benefit from the use of the product. So I mean I think those are all relevant conversations and discussions to have. I feel like we're still early in the process and I don't think the notion is that this is like the panacea to solve the issue of youth tobacco use, but it's one novel type of technology that has been raised and discussed with us and I think we just are very open to continuing those conversations.

CDR. RUSSELL: Thank you. Do we have any questions from the audience? Come on up, sir.

MR. SOLYST: I was here a few minutes ago. Jim Solyst. I'm a consultant.

Dr. Farrelly, your opening response was about factors in APPH, so I gather there's not going to be a definition of APPH posted on the website. But there certainly are factors. And I've written articles in the past; I hope I wasn't terribly wrong. I'm sure parts of it were wrong, but I always would say that you're not going anywhere unless you have low levels, or sufficiently low levels of HPHCs. And so that would be an example of a factor that would be part of achieving APPH. And I imagine there's others like that that you could name that -- I mean much of what we've discussed over the last day-and-a-half I assume go into the APPH process.

But if you could elaborate at all -- on the example of HPHC there is a starting point. You're not going anywhere without meeting a threshold. And then it's by a case-by-case example going forward. Is that fair to say?

DR. FARRELLY: Yes, I think that's fair to say. As the presentations talked about, HPHCs are a component of that. We also learned about leachables,

and then also ingredients themselves. So all of those are factors that could enter into the risk profile as our colleagues from toxicology discussed.

And then on the other side of course of factored is the benefits. How complete -- what's the magnitude of the switching away from a tobacco product with a higher risk toward one with a lower? What's the magnitude of that? That's clearly a factor for us. Then the appeal for youth and youth use. That's another factor.

So you're right, we could articulate all those different factors, put them all in one place. And that is one of my goals is to better articulate all of those different factors so the applicants can be more aware of what those types of tradeoffs are. And I think the thing that we have ongoing conversations internally is just that, because each product has its own profile, both in terms of risks and benefits and they all are very different.

But the factors that you mentioned are definitely the ones that are central to those decisions as well as we had other conversations about abuse liability. That impacts both adults, but also

new initiates and how that factors their pattern of use over time. So hopefully helps add a little granularity to the answer on APPH.

And feel to jump in, folks.

DR. CECIL: I was just going to say damn, seven months, I'm impressed.

DR. FARRELLY: The training wheels have come off.

CDR. RUSSELL: Do we have any additional questions from the audience?

This question is in reference to shelf life, and this is from the virtual audience. Can you elaborate on the amount of products that need to undergo stability studies? For instance, if an application is for 10 products varying in flavor and nicotine strengths, is it possible to bridge the shelf life based on a few products that undergo stability studies?

DR. ROGERS: I'll take this one. So the stability data is really going to depend on your particular product. So we have seen applications for e-Liquids in multiple flavors where the applicant was successful in bridging from certain flavors to

additional flavors, and in these cases they gave us a very detailed description of how the ingredients of the tested products would bridge to the untested products. So that is one example that we have seen where someone was able to do that. So it really depends on the characteristics of your product.

CDR. RUSSELL: Thank you. The next question references deficiency letters. Upon receipt of a deficiency letter from FDA will applicants have the opportunity to ask for clarifications about the deficiencies if needed? If yes, will FDA's time for the subsequent response count against the applicant's 90-day window for addressing the deficiencies?

DR. STARK: The timeline for the deficiency letter starts with date of issuance. We know that we are still physically mailing. And I call it snail mail. It's quite slow, which is why we traditionally will have a project manager reach out and offer a courtesy copy. We can't just plop it into email because of risk of being hacked, so there is usually a standard set of questions to make sure we can release that.

With respect to clarification yes,

absolutely. If you require clarification for your deficiency letter, let us know. Our goal is to get you a response to that as soon as possible since the clock is ticking. If there is for some reason a major delay that could significantly impact any type of testing or other type analysis, we'll look into that case specifically, but in general the 90 days starts from issuance of the deficiency letter for a response to FDA. Thanks.

CDR. RUSSELL: Thank you. Do we have a question from the audience?

MS. HO CHEN: Hi. Angela Ho Chen, independent consultant, FDA Regulatory and Legal Services. I've sat on both sides of the fence. I want to give you a softball question: In response to Dr. Farrelly's comment about internal deliberations on more clarity and more transparency, when should we expect that from FDA and what form will that take? Is it going to be in guidance, regulation, something on the website?

It makes it really hard to advise our clients; and I know you've heard this before and I've heard it on both sides, in terms of the cost for doing

studies, especially like the RCTs and the clinical trials. They're quite costly. Even some of the inhalation tox studies run millions, so just to give you an idea. So it would help us to help you.

DR. STARK: Okay. So the questions are always simple; the responses not as much so. In general we're looking to have multiple modes of communication to provide updates. Some of those may be in the form of quick updates to our website either through redactions quarterly for some of our past decisions. Yesterday I committed to looking into as well as some decisions that we could put up that are generalizable which may hit on some of the needs for studies and other types of testing that wouldn't violate any trade secret or CCI information.

We will also have updates through some of the regular communication from both Dr. Farrelly and Dr. King. There will be communication in the forms of guidance or rulemaking as it's made available, as well as communication through public meetings such as this, potential workshops, or other types of fun meetings that may come up.

What I do want to stress is the amount of

time that it takes and the clearance on our side to make something publicly available. While we can speak freely to a certain point either here or on a call about a specific case, when we're putting out information to be broadly used we do want to follow all of our good guidance practices, go through clearance properly, ensure it's vetted, and placed out in a timely manner. Timely manner for that process doesn't necessarily match a timing manner for a normal lay person. So if you're looking in terms of a guidance or rulemaking, that could take a couple of years, just so folks have a sense. Qs and As on our website can take up to six months. Redactions, when it goes through our 508 compliance process, can take a couple of months. So I just want to give you guys a sense of why it make take so long for something to come out.

Some of the public remarks from our senior officials may be some of the fastest ways that you see it and some other statements when we make decisions.

Anything else to add from others?

CDR. RUSSELL: Before you, sir, I think we have one other question before you, sir.

MR. FISHER: Sorry.

CDR. RUSSELL: No problem.

MR. CHAUDHARY: Hi, Naveed Chaudhary, Broughton Life Sciences. I've got two questions, but I'll keep it to one. Given all of the data that's been generated so far across 1,000 pounds of applications that have been submitted is there going to come a point whereby it becomes obvious if there's no combustion the levels of HPHCs are lower, therefore the toxicity associated with it must be lower and therefore the toxicology focus is just on ingredients? Do you think that time will ever come and how far do you think we are from that time?

DR. CECIL: Every individual product has to be assessed for its individual combination of risks and benefits. That's required by the law. And so even though you may say a product is only the ingredients, we need to look for the issues if we're still looking for other things that are cropping up that we have be aware of. Diethylene glycol is a perfect example. EVALI was an example where things show up that are not clearly obvious when we start looking at ingredients that there's going to be a

significant health risk. So I think we have to look at each and every application individually and assess each one and see where on the continuum of risk it lives. I think making an assumption that all of them lived on one end or the other end is going to be problematic.

Now admittedly each category is going to be different, and look at the categories of the products themselves, and some of them are lower risk than others, but it's not a very small margin. There's going to be overlap always. And so there's -- making a presumption is something that we just aren't comfortable doing, even when there's a lot of data. We don't do that with cigarettes, and we've had a lot of data on cigarettes. When we look at an SE there's a lot of assessment of everything that goes along with those.

So I don't think that FDA will, at least in the short term, be in a position where we're comfortable making an assumption about a whole category or a whole type of product.

DR. FARRELLY: I was wondering though if you're getting to more of a notion of collective

knowledge.

MR. CHAUDHARY: Yes, I am.

DR. FARRELLY: Yes. And I think when you're talking about collective knowledge it -- as we make more determinations and more information is out there, then of course the savvy applicant will be reading all of those and making decisions about the profile of their products accordingly. We won't necessarily be saying this is where you need to be, but the bread crumbs will be on the trail for you to follow as the body of evidence and body of information increases.

So I think the answer to your question is yes. When that will be, that's harder to say, but I think that everything that Dr. Cecil said is completely true. Our job is to look at each individual application and the information provided. Over time you'll be getting signals and more signals and those signals will guide you one way or the other and which will likely increase your chances of getting a positive order. So I read your question in that way and I think that that's what you're saying is true.

MR. CHAUDHARY: Yes.

DR. FARRELLY: Putting a timeline on that, you'll never get us to get concrete timelines for that because there's just too much uncertainty about what we get as well as the other constraints that Cristi mentioned.

MR. CHAUDHARY: Yes. I then have a second question --

CDR. RUSSELL: Go ahead. You may proceed.

MR. CHAUDHARY: -- thank you, which is more of a philosophical one, I guess. I'm going to wave the flag for my home country, the UK. And as you'll know the DHSC published some thought last couple weeks around how they want to regulate e-cigarettes and other products in the UK. Have you had any inspiration from what the UK government are trying to do and the DHSC are trying to do as well in terms of framing your thinking?

DR. FARRELLY: I guess it hasn't made it across the pond to my inbox yet, but maybe my colleagues have looked at it.

DR. STARK: What I will note is we take note of different policies or planned policies around the world, but we do have certain constraints and laws

that we have to follow here within the U.S. So we try to have lessons learned. That's kind of part of FDA history, why you'll see some differences between what we do here and across the pond. We also are looking to put forward reasonable policies when it makes sense for all. So it's safe to say under review, but no changes based on what you've heard here.

CDR. RUSSELL: Thank you. We have another question.

MR. FISHER: Hey. Michael Fisher, Juul Labs. Last spring Dr. King had said you all were going to start posting the reviewer guides again, which are super helpful. So how's that coming?

DR. FARRELLY: Well, I mean that's also related to the Reagan-Udall recommendations and we're fully committed to doing that. And it's a work in progress. It's definitely something that I'm very aware of as the office director. So it is a regular agenda item for our management team and it is something that I want to get out there as fast as possible. Fast as we can manage it.

(Laughter.)

CDR. RUSSELL: Any other questions from

our audience?

MS. HO CHEN: Angela Ho Chen again. This might be a tough question. So in terms of the way that the statute structures the premarket review from SE, SE exemption to PMTA, right, and APPH standard, have you guys thought internally about the history of why that was created and our evolution in terms of how we review products? So when you look at the spectrum of harm or continuum of risk is there an opportunity here to reevaluate whether it's through policy, rule, guidance how we interpret APPH in terms of the innovative products?

If you have cigarettes on the most harmful side of the spectrum there's an underlying assumption that the innovative product, right, depends on what side of the fence you sit, whether it's in a place of trust or distrust. Is there an opportunity here for harm reduction to reevaluate how you look at APPH so it gets to the standard and what do we need?

DR. FARRELLY: I will take a stab at this and will welcome my colleagues to join in.

I mean, I think even with the PMTA rule in and of itself there's plenty of opportunity for

innovation and for our framework to factor that in. The age-gating technology is one example of how you can reduce one of those factors of risk, right?

But any product that comes in with the potential to be lower risk from a toxicological and other health risk factors, I mean it fits right into the framework. It may not be as explicit as everybody wants, but there's plenty of room for innovation, there's plenty of room to move to have products authorized that are a lower risk. I don't think it needs radical reinventing of the rules that we have now to move the population down the risk continuum. So to me that's not exactly a hard question.

If we had to do it all over again starting today, would it be different? I'm sure it would be different. We know a whole lot more now than we did in 2009, but as my colleague Cristi already mentioned, the time it takes to set up new rules and guidance is very lengthy. And I think that you have to think about the tradeoffs between establishing new guidance and working with the ones that we have and I think there's plenty of opportunities to improve public health with the framework that we have now.

CDR. RUSSELL: Thank you.

DR. STARK: So I'm going to add one more item. I just want to be clear. The standards themselves are set by statute for our premarket pathways. How we interpret the data to reach that finding is what can change with time. So when we look at APPH for an exemption pathway for PMTA we have various factors in the statute that are already set that we have to address. It's just the interpretation. I just want to make sure that's clear.

CDR. RUSSELL: We have another question from the audience.

MS. BOOTH: Hi, Kellsi Booth, Turning Point Brands. So we have talked a lot about ENDS applications specifically over the course of the past days, and I think that makes a lot of sense just given the volume of applications, but there are really interesting new and other innovative product categories.

And my question is if you are considering or would consider developing more documents like the ENDS guidance for categories like modern oral.

DR. CECIL: I think that the concepts of APPH are going to be common across all of the different types of products. The details are going to be different depending upon the individual application of -- both in terms of the category and in terms of the application as provided.

So will there be specific guidance or specific rules or changes for modern oral? At this point in time I don't know that there's any planned. I know CORESTA's working on some things, which is fabulous. Great. We'll be watching that with great interest, but I'm not sure that we expect to see anything in the near term that will address that again.

And I think Cristi was being very polite in calling guidance taking two years. The fastest guidance I've seen move is five years. The TPMP is what, 12 years now that it's finally -- so I think it takes an extended period of time rather than a short period of time.

MS. BOOTH: And I do get that. And I'll just say that I have probably 100 very highly technical specific questions that I would love to ask

on this, so perhaps another workshop with more specific focus on those areas of interest could be a great forum for that discussion.

DR. APELBERG: Yes. Yes, I mean I was just going to add a few things: one is I think, as we announced at the beginning of this two-day workshop, in response to the Reagan-Udall Foundation one of the things we're asking for is input on what you all think would be the short of highest priorities with respect to guidances or kind of information that would be useful to hear from us. And so that -- I think there was an email address that was put out to send that information, so we will definitely consider the recommendations that come in for the center as a whole.

And I think that like Dr. Cecil said, ultimately our APPH analysis is about risks and it's about benefits and regardless of what product you're talking about. But we've also talked about that to the extent that the toxicity, the risks are lower, to the extent that youth appeal and youth initiation risks are relatively lower. Then it also sort of has implications for the magnitude of the benefit that we

would want to see to be confident that the benefits outweigh the risks. So these things are all kind of interrelated, but we appreciate the question and the opportunity to have more conversation about that.

MS. BOOTH: Thank you.

CDR. RUSSELL: I will provide that email address for topics that you would like to suggest for FDA for future workshops. It's CTPregulations@fda.hhs.gov.

We'll take one more question before we take a few questions from the virtual audience.

MR. HOLMAN: Hello. Matt Holman, Philip Morris International. Thank you for hosting this two-day meeting. This is really helpful and useful. I know it takes a lot of work to put this together. I appreciate all of that work that you guys put into this.

I have a question around performance metrics. I know that they're challenging to sort of track all the work that's being done and to be able to report that out to the public, but they are really useful. It seems like in the past 14 months-ish; I randomly picked that time point, that there's not been

a regular frequency of reporting them and I wondered whether you guys would be going back to report on them on a regular basis.

And also thinking about them I think they're really helpful and that they're really good goals to set to sort of make sure you guys are meeting the marks that you want to meet, but obviously also helpful for the public to kind of know where you're at in the status of what's a very, very big backlog.

And so I wondered whether you're thinking about different end points to measure; I know firsthand that those end points have changed over time as the situation has changed, and try to come up with more meaningful end points that you are reporting on, but wonder if one -- or I wonder if some metrics along the lines of how many actions you guys take on say non-combustible products relative to combustive products might be a more meaningful end point rather than the just time frame to review, because at this point time frame review is really complicated by again the huge backlog.

But I wondered whether you guys could come up or thought about coming up with performance metrics

that better align with sort of the public health mission and things along that line. So again, thinking about how many actions on products that potentially further down the continuum of risk than combustible products. Thank you.

Cristi, I think this was mainly for you.

DR. STARK: I know. I'm looking to see if Matthew wants to jump in.

So yesterday I did note that there have been some delays with posting for the metrics. We've moved from weekly when Dr. King started to every two weeks to every month to quarterly. Some of the quarterlies have been delayed. I'm calling that out. You know that I'm pretty transparent about that.

The goal is to go towards quarterly reporting to match up with some of the other centers, FDA reporting like FDA-TRACK and everything else. With respect to other types of measures I'm interested and open to other types of metrics that might be reasonable for people in the public to understand and track.

I'll be working closely with Yuan to see what's possible with our systems that could be

meaningful and relate back as well to some of the required congressional reporting and the current metrics. I want to make sure it's an apples-to-apples comparison when we're using numbers, but I'm open for feedback on other types of metrics that may be reasonable.

MR. HOLMAN: Great.

DR. STARK: Thanks, Matt.

MR. HOLMAN: Thanks.

CDR. RUSSELL: Thank you. We will take our next question from the virtual audience, and it's in reference to the SE queue.

As FDA works through this queue it is -- if it reached an applicant's turn for prioritization but their only SE report is a post-rule submission, will FDA skip the applicant until it works through the other applicants' pre-rule submissions? Is there a way for applicants to prioritize post-rule SE reports or do they need to wait until these reports are accepted?

DR. STARK: I think that one's mine again.

Okay. So what was presented yesterday by Kris VanAmburg was a proposal regarding some new

thinking around SE queue prioritization. The current queue is a static list, as Kris noted, so it is based off of applicants, the 105 applicants that submitted deemed applications. And if all of their applications have been complete, we skip to the next one.

The proposal yesterday, which we're open to feedback on; it's one option, would be a dynamic list that would include the bolus and post-bolus and we would look for industry feedback for what's most important, which means industry could provide a list for a post-rule application to come before a deeming or a pre-rule application. Part of it is understanding what's important. And we can factor that in when we're looking for selecting the 25 to go towards that review team for scientific kickoff.

I hope that was clear. If not, I'll look for a clarification. Thanks.

CDR. RUSSELL: Thank you. We'll do one additional virtual question before we move to face to face.

The next question is from a toxicology perspective. Is a positive genotoxicity outcome or any other toxicity in non-clinical testing completely

unacceptable in ENDS? It may be possible to design a product that has eligible -- ineligible toxicology risk, but if such a product is not desirable and does not result in switching from more harmful products, would that still be desirable?

DR. ROSENFELDT: So I think I will start with the toxicology part of this and then let our director speak about the larger issue of APPH.

So toxicology describes the harm, the potential harm, the risk of a product. Right now tobacco products carry risk. And the PMTA rule, the ENDS guidance, TCA -- they require -- well, the law requires, the rule requires that we describe, fully describe the harm or the toxicological risk from the product. After that it goes to a larger issue where there is a risk/benefit thought process. And I will shift it to your director.

DR. FARRELLY: I mean I don't have a whole lot to add besides that because we have talked about that. Once we've been able to assess the toxicological and other health risks; that's that side of the equation, then it behooves the applicant to demonstrate the benefits. Of course then the tricky

part is how do we weigh those risks and benefits? And with the way that question was stated I don't know that there's much more for us to say other than you also have to show benefit for that product relative to other tobacco products such as cigarettes.

CDR. RUSSELL: Thank you. Next audience question?

MR. GILLILAND: Hello. Thank you. Stan Gilliland with Consilium Sciences Consulting. I had a question that revolves around switching studies. So it was brought up today about demonstrating an additive benefit for menthol or other flavors over tobacco and switching. And I want to be heard clearly that my reason for asking this question is to better design studies moving forward.

Have you put a metric on what the I'll call it additive risk of menthol is over tobacco to youth so that we can properly power our studies for switching studies? And the second aspect of this is as we're switching to products not on the market have you considered the logistics of distributing products to consumers to test switching, such as the PACT Act and companies being unable to deliver products to a

consumers' house?

DR. APELBERG: I can start. I think the first part of your question sort of gets back to the conversation we had in the earlier panel about kind of like the threshold, sort of how much greater benefit in terms of switching are we looking for or are we expecting? And what we talked about there is that really because there's sort of like multiple dimensions that we're evaluating at the same time when we're making our APPH determination there's not some specific threshold.

What we've articulated is that because of the higher risk of youth initiation/youth appeal of non-tobacco flavored ENDS products that we're looking for greater evidence of benefit. And that includes both kind of having the strongest study designs to evaluate that, which is why we talked about longitudinal studies, whether it's a trial or an observational study. And then also have that be put in the context of a comparison with the tobacco-flavored ENDS because the extent to which, for example, a tobacco-flavored ENDS product could provide the same benefit to a smoker without increasing the

risk to youth, I mean that has implications for our decision making. So that's really the framing.

I terms of logistics, I mean I think there's a lot of considerations. One we talked about just generally in a premarket context, a truly premarket context. There are certain constraints on what can be done. You're basically going to be doing some kind of intervention whether you're giving people products to use or randomizing them and asking them to use it in a certain way. And we have the ITP process for reviewing new studies, clinical studies for using products that haven't been marketed.

But I think it's -- I don't sort of have too much more to add from what we talked about in the previous conversations in terms of kind of the basis for why we're looking for this stronger evidence, but if there are some specific issues that are challenging in terms of implementation like we've talked about, there are mechanisms by which we can have a meeting before an applicant submits a submission to really talk through the strengths and weaknesses of different approaches to conducting these kinds of studies.

DR. FARRELLY: And the other part of your

question had to do with the PACT Act, which isn't really of course under our control or purview. That act was passed by Congress and the larger context for the PACT Act was to reduce a number of different illegal behaviors. One, which is shipping cigarettes for example from low-tax jurisdictions to high-tax jurisdictions as a way for consumers to avoid high taxes. The other thing that it was intended to do was to reduce youths' ability to purchase cigarettes online, having them shipped to their households.

So I know that that adds constraints to the situation that you're talking about, but that larger context is something that also impacts public health. I know that I haven't read that rule, that act in a long time, but those are factors well beyond the purview of FDA. Maybe what you're asking for is there some way to carve out exemptions.

MR. GILLILAND: Yes.

DR. FARRELLY: Yes, again I don't know that that's necessarily something that FDA is totally in control of.

MR. GILLILAND: Yes, not pointing fingers. And this last part of this question is -- talked

about the holistic review of the application, which is not just switching studies. So companies develop their portfolio to reach the most consumers as they can, and it's not a one-size-fits-all. Does that play into your decision when you're evaluating the switching studies results? So a tobacco may work really well for one set and a menthol may work for a very different set of a population even if they have the exact same switching percentage. So how do you grapple with that?

DR. FARRELLY: I'll start and then Ben can think.

So I mean APPH -- in that APPH is public health. So the population health, the reach of a product is relevant, right, because we're weighing the benefit of moving people away from riskier products. But then also of course if a product has large market reach for your intended audience, that could bring along with it additional youth risk, which we have to assess as well. So we're looking at the population level risks and the population level benefits.

Making that translation from an individual application for an individual product and its specific

effectiveness of switching, for example, translating that to public health and then weighing it against the risks and benefits is part of the challenge that we have to do. So we do factor it in and take that under consideration, but -- and we've had many conversations about this, so hopefully Ben can add some granularity to what I just said.

DR. APELBERG: Yes.

DR. FARRELLY: I bought you time though, so --

DR. APELBERG: No, I mean it's a good question. One of the ways that you could potentially get at the issue is to consider like are there particular sub-populations, for example, of adult smokers for which you have reason to believe that certain types of flavors would be more effective and kind of either stratify the analysis or conduct separate studies among those individuals.

I mean there are probably designs where you have to be thoughtful about in a trial would you randomize the one flavor versus another, or even potentially the option to choose from different flavors? I think there's different sort of ways to

gather the evidence so that we have some empirical basis for being able to see that clear evidence of positive effect and additional benefit. So but it's a good question.

MR. GILLILAND: I know I hit you with a hard question, so thank you.

CDR. RUSSELL: Thank you. Next, sir?

MR. VADERS: Hi. Mark Vaders with Womble Bond Dickson. I had a clarifying question about the reviewer guides. Correct me if I have a misunderstanding, but it sounded like from your previous comment like you are in the process of reviewing and updating your reviewer guides in anticipation of releasing them publicly. And I applaud you for doing that. That's great that the agency is updating its reviewing guides in response to new learnings and additional data and things like that. But I also know that there are numerous FOIA requests outstanding for current reviewer guides at various points in time including the reviewer guides that have been used to make determinations on products that are now legally marketed.

So is there a reason that we couldn't get

those with the caveat that the agency's thinking may have moved on since they were current?

DR. STARK: He punted to me. I do know there's a backlog with FOIA right now, and I can't comment what that is. I'd have to check with my colleagues in the Office of Health Communication and Education.

Traditionally when there are a large number of FOIA requests we do try to make it available in our reading room. It just shows -- it's a point in time regardless if the thinking has changed. So I'm happy to follow back up with Marquis (phonetic) and her staff to see where that is.

I am going to turn it back to our office director though to talk about the rough recommendations with respect to the reviewer guides. I'm going to note that we're looking at all the reviewer guides with trying to make as much publicly available as possible. And I'll let Matthew talk a little bit more about timing.

If there's anything you can add. No?

DR. FARRELLY: Not really a whole lot, but we've been talking about this a lot. And there is a

backlog and that is concerning to me. And so I want to talk to our colleagues and strategize about what are the capacity constraints? Where in this whole chain are we hitting bottlenecks and what can we do as an office to speed this along? Because those kinds of things just generally frustrate me. That's just in my nature.

So there was an exchange I had with somebody about this this morning. So it is something I'm committed to looking into and seeing if we can just speed up and shorten that backlog. Other than that I can't give you details other than I heard you and I'm sensitive to that question and I want to do better.

MR. VADERS: Thank you.

CDR. RUSSELL: Thank you. We have a few questions that are from our virtual audience that came in yesterday. And this is from an engineering perspective, and it's engineering product design and it's going to be a three-in-one question.

FDA requests that applicants include a description of problems identified in prototypes that are subject to the studies contained in the

application or previous or similar versions of the new tobacco products that were marketed. If any what constitutes a problem for purposes of this section, the prototype bibliography?

What results in a previous or similar version of a product for -- I'm sorry. Yes, what results in a previous or similar version of a product for purposes of this section?

As novel products are brought to scale is it reasonable likely -- is it reasonably likely that manufacturing processes will change? For example, manufacturing steps that are initially manual may become automated? What data does FDA expect to receive in a PMTA if any to demonstrate equivalency through the development and commercialization process?

DR. MORSCHAUSER: Thank you. So in the PMTA final rule a problem includes overheating, fires, explosions, as well as any information regarding manufacturing to the product -- manufacturing issues relating to the product such as packaging defects that could pose a health risk.

The terms previous or similar version or prototype mean any previous generation, model, or

version of the tobacco product that has undergone testing or was on the market in other countries such as first generation ENDS products that underwent aerosol or battery testing and were subsequently modified as a result of the testing, adverse experiences, or design concerns that could impact public health.

The FD&C Act requires the PMTA to contain full descriptions of the methods used in the facilities and controls used for the manufacturing process, and when relevant the packaging and insulation of the tobacco product.

The FDA's interpretation of this requirement together with its authority under Section 910(b)(1)(G) of the FD&C Act states that these descriptions must include information regarding all manufacturing facilities including a description of the designed controls and be sufficiently detailed to demonstrate that the product meets manufacturing specifications and can be manufactured in a manner consistent with the information submitted in the PMTA.

The process by which a tobacco product is

manufactured is important to FDA's determination of whether or not a new tobacco product is APPH because it demonstrates the likelihood that the tobacco product that will ultimately be used by the consumers meets the specifications set forth in the PMTA.

For a new tobacco product under review new manufacturing information; for example, addition of a new manufacturing site for primary and secondary processing or a change in a manufacturing step or process to address a quality or safety issue not initially provided in the application, may be submitted as a major amendment.

For products that have received marketing or granted orders manufacturing changes will be review on a postmarket basis. Reviewing the manufacturing changes will allow FDA to determine whether or not they result in a modification, intentional or unintentional, to the product and is therefore -- would be therefore a different new tobacco product without premarket authorization.

CDR. RUSSELL: Thank you. We have another question that came in yesterday from our virtual audience, and this is an environmental question. Why

did CTP write environmental assessments for some PMTAs? Is this something we could have asked CTP to do for our application?

DR. HANNA: So I'll take that one. According to 21 CFR 25.40(b) FDA requires an applicant to prepare an environmental assessment and make it -- and make any necessary corrections to it.

When evaluating the submitted EA and making a determination whether there are significant environmental impacts or not, CTP makes a decision as to use the applicant's EA or prepare one with additional information.

This decision is based on a number of different factors including if all of the information we deem necessary is included in the documents, if the documents contain confidential markings, if any information we disagree with our deem incorrect is included in the environmental assessments, and if there are any mistakes in the documents.

If the applicant's submitted EA is missing information, we may ask the applicant to submit a revised EA that includes the requested information or we may write an EA. Submitting a complete and

accurate EA with your application helps applicants to avoid delays caused by CTP having to request information or edits from the applicants.

DR. STARK: I'm going to add one point to that. If you look in all of our rules right now -- and we actually have a requirement; look at the PMTA rule; look at the SE rule -- you must have an EA present. As was discussed prior the only types of categorical exclusions that we currently have are for provisional SE products or for negative decisions. So it's imperative if you want to get your application accepted to include an EA in the application. Shannon went through some of the cases where even with the EA present FDA will write one on the applicant's behalf. Thanks.

CDR. RUSSELL: Cristi did just state this, but just for anyone who is uncertain I will read this question as well. A separate environmental assessment reports -- are separate environmental assessments reports required for each new tobacco product or may multiple products be covered in one combined report? I think this one is for Shannon.

DR. STARK: Okay.

DR. HANNA: So as Cristi mentioned, an EA must be prepared for each action, not categorically excluded as per 21 CFR 25.40(a), and while it's preferable to submit a separate environmental assessment for each new product, a combined environmental assessment is acceptable as long as it lists all products that are the subject of the prepared EA.

Individual environmental assessments allow for an accurate assessment of the environmental impacts of the proposed actions if not all the products receive marketing granted orders. If the applicant submits a combined environmental assessment and one or more of the products do not receive marketing granted orders, that affects the assessment.

CDR. RUSSELL: Anything you want to add, Cristi?

Thank you. So we have approximately about five more minutes. I will read two additional questions that came in from the virtual audience from yesterday and ask any additional questions of the live audience.

So this question is in reference to oral

nicotine products. And this is about three questions in one. FDA received a few questions relating to oral nicotine products that we combine to avoid duplication. What is FDA's criteria for demonstrating that oral nicotine products are APPH and what factors does the agency consider?

Given low youth use and low relative risk HPHCs in oral nicotine products when would these products not be considered APPH?

What would an appropriate comparator product be for a modern oral pouch and is a cigarette a valid comparator?

Lastly, how does FDA evaluate HPHC risk comparison between cigarettes and modern oral pouches? That was five. Sorry.

DR. APELBERG: I can start. There was a lot packed into that. But I mean this question kind of gets at the question that was asked earlier about oral nicotine products. And what I had communicated earlier holds now as well, that really the APPH analysis is the same holistic analysis that looks at risks and benefits to the population.

And so as I alluded to earlier and we've

talked about previously as well to the extent that an applicant can demonstrate risk, whether that's the toxicity, other health risks that are lower on the spectrum, can demonstrate a lower appeal and a lower risk for youth initiation, that also has implications for the magnitude of the benefits that we would want to see to be able to ensure that those benefits outweigh the risks. So it's that kind of weighing.

And but this question also asks specifically about comparator products. And I think we've talked about this in a variety of other contexts that really -- there's usually sort of multiple comparator products of interest and it really is a function of understanding who the products are intended to be marketed to as well as who are generally going to be the types of individuals that are more likely to use the product.

So oftentimes one comparator will be cigarettes because a company will propose to market a product as an alternative to cigarettes. And so we'd be looking for comparative data there including both levels of harmful constituents and risk and also obviously the extent to which adult smokers would find

the products appealing and switch to them.

But in addition typically products within the same category are also important comparators for a few reasons including the fact that oftentimes those may be -- individuals using other similar products may be the most likely actually to use a new tobacco product. So that's why oftentimes I think throughout the presentations we've talked about, and what's laid out in the rule and in other documents, sort of comparators both within the product category as well as to products outside the product category, oftentimes cigarettes is what we're talking about in that comparison.

So hopefully that -- I don't know if I answered all the questions. There were a lot there.

CDR. RUSSELL: We have another question. It came in from yesterday, and this one is for -- about eSubmitter and forms. Does the FDA plan to further expand on the electronic tobacco technical document, ETTD, structure for PMTAs especially by adding additional granularity to the table of contents beyond the first level structure currently available?

Will the XML backbone specifications eventually be created similar to the ECD -- ECTD XML backbone?

Does CTP plan to develop an ETTD technical guidance document in the future?

MS. TIAN: Okay. I will pick up this question. So first, yes, we keep working on, to expanding the table of contents. We provided in the electronic submission, specific file formats and specifications. So even though three years ago we provided the table of contents only for two levels, but that takes a lot work. So expanding to a deeper level is similar situation. It takes a lot of effort, a lot of work to do it, but we will keep updating the electronic submission file format and specification documents. If we will have any progress on this -- on the deeper level, kind of modules, we're going to sharing in this documents.

Talk about the ECTD, the XM -- XML backbones, okay? There's actually also exploring different submission standards right now. So depends on the future standard we are taking. We may need XML backbone. We're making adjacent. So it's different

kind of for future or main use. We will keep this also open, transparent. Also we're open to the public feedback, industry feedback. If you have any suggestion, please feel free to reach out to us and share your opinions on this. So I think I answered all the questions.

CDR. RUSSELL: Thank you.

Sir, I'm going to call you up, but I don't want your colleagues to be upset with me because it is 3:59. But you ask the last question.

MR. BARKER: Hey. Good afternoon. Eric Barker with Altria. As the use of device technology grows and advances, and we've talked a little bit of it the last couple days, how is the agency thinking about things like software updates or fixes for bugs that do not change sort of the core APPH characterizations we've been talking about? Thank you.

DR. MORSCHAUSER: So I think for some of that it goes back to what I touched on a little bit earlier in that it depends -- things like that will be looked at probably in the postmarket. And depending on the level of change required there, whether it

changes the functionality of the device, it would have to be reviewed in a case-by-case basis. And then whether or not it does change the functionality of the device would determine not -- whether a new application would need to be submitted or whether it would just be an update.

MR. BARKER: Thank you.

CDR. RUSSELL: So we did have one more question that came in through the virtual chat, however we will respond to that question and post it to the FDA website. This now concludes the question and answer period for the open public meeting.

Before I depart I would like to thank all of our constituents, all of our stakeholders for joining us today.

Thank you, panelists, for doing the hard work of answering those questions, and live.

And I would like to thank you guys for spending the day with us for the past two days. Thank you all.

As a reminder, if your questions did not get answered during the panel discussion, you can ask additional questions and you can submit them to

askCTP@fda.hhs.gov.

I will turn the floor over to Dr. Apelberg for our closing remarks.

Dr. Apelberg?

DR. APELBERG: Yes, I'll just do it from here, if you don't mind.

(Laughter.)

DR. APELBERG: I'll just be brief because it was a long day today, but it was a really productive day, as was yesterday. So I just wanted to take a few minutes to thank you all for participating. That includes those in the room as well as the many people who joined us online, and specifically the people who asked us questions. We really appreciate hearing from you and being able to provide answers to those questions. So we really just hope you got as much out of this meeting as we did.

Over these days we've tried to provide more clarity on a range of administrative, technical, scientific issues that come up in premarket applications, really spending some time talking about FDA's experience so that we can kind of provide that information to you all. And hopefully you'll find it

useful as you move forward in the application review process. I know we touched on reiterating some of the requirements that are out there as well as talking about some new tools that we've put in place to try to improve efficiency.

So I just wanted to -- before closing out just reinforce what Dr. King and Dr. Farrelly had talked about in their remarks that we're really committed to engaging with you all, with stakeholders and being as transparent as possible, and this dialogue is an important part of that. So just keep an eye out for future opportunities to continue to engage, for us to share our progress, improvements we're making on the process and the program in general as well as opportunities to answer additional questions.

So just as a reminder, the meeting has been recorded. It will be made available on the FDA website. If you have any additional questions, you can email us at askCTP@fda.hhs.gov.

So with that I'll just say thanks again for being here. For those that are here, safe travels and we'll see you again soon. Thanks so much.

(Whereupon, the above-entitled matter went off the record at 4:04 p.m.)