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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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THE PREMARKET TOBACCO PRODUCT APPLICATION FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS): A PUBLIC SEMINAR

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October 18, 2016
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3501 University Boulevard East
Hyattsville, MD 20783

FDA:

CAROLYN DRESLER, M.D., M.P.A.
Associate Director for Medical and Health Sciences
Office of Science
Center for Tobacco Products

KIMBERLY LINDSEY, M.D., M.A., CAPT, USPHS
Medical Officer, Division of Individual Health Science
Office of Science
Center for Tobacco Products

II-LUN CHEN, M.D.
Director, Division of Individual Health Science
Office of Science
Center for Tobacco Products

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Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

SESSION 5: HUMAN FACTORS AND LABELING

JAMES CHENG, M.S., CAPT, USPHS
Senior Engineer, Division of Product Science
Office of Science
Center for Tobacco Products

PRISCILLA CALLAHAN-LYON, M.D.
Deputy Director, Division of Individual Health Science
Office of Science
Center for Tobacco Products

SESSION 6: ADDICTION AND ABUSE LIABILITY

CHAD J. REISSIG, Ph.D.
Addiction Branch Chief, Division of Individual Health Science
Office of Science
Center for Tobacco Products

MEGAN J. SCHROEDER, Ph.D.
Lead Pharmacologist, Division of Individual Health Science
Office of Science
Center for Tobacco Products

SESSION 7: INITIATION, CESSATION AND CONSUMER PERCEPTION

BENJAMIN J. APELBERG, Ph.D., M.H.S.
Acting Division Director, Division of Population Health Science
Office of Science
Center for Tobacco Products

DAVID B. PORTNOY, Ph.D., M.P.H.
Supervisory Social Scientist, Division of Population Health Science
Office of Science
Center for Tobacco Products

KATHERINE A. MARGOLIS, Ph.D.
Social Scientist, Division of Population Health Science
Office of Science
Center for Tobacco Products

PRISCILLA CALLAHAN-LYON, M.D.
Deputy Director, Division of Individual Health Science
Office of Science
Center for Tobacco Products

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M E E T I N G

(8:30 a.m.)

DR. DRESLER: Welcome to the second day of our information seminar on premarket tobacco applications.

Just a couple of housekeeping notes. As you've probably seen as you walked in, there are multiple meetings that are here, including one that's across the hall, and they have enticing looking food, and I have been tempted myself. But please know that is not our food, and we cannot provide food at it, and that's not ours, and you can imagine they get unhappy when they see us snacking at it. So please, that's not food for this meeting.

The other thing, too, is that as you may have noticed, not all questions that you may write and put onto the cards may get asked. And so we've had comments both from people in the room and online, and that's because we are staying very strictly to sharing information about the guidance and the draft guidance that's out for comment. And if any questions are product specific or they're policy sort of questions or they're not within the scope of the meeting, then you're correct, we're not addressing them here. And so we would urge you, if you had any of those questions or if you wrote a question and you really

want those answered and you didn't get them asked and answered either yesterday or today, please send them in to the website, okay, AskCTP. That would be a much better place for those sort of questions.

And the other thing, too, is that we're working on combining questions so that I'm not up here repeating them, because you all will think I'm really stupid if I'm repeating the same question over and over again. So the team is helping me by combining some of the questions if they get to be the same.

So with that, Dr. Lindsey, was there any comments that you wanted to give?

DR. LINDSEY: Good morning. I just wanted to remind you that this seminar is being recorded, and you will see on some of these slides that you're going to see today some resource links. Again, for those of you who are here in person, we do have copies of those outside the room, along with the agenda that you can pick up. And for those of you who are online, we will try to make those copies available, and then they will have activated hyperlinks. So don't spend a lot of time trying to write down all the resource links as we go through the presentations because that information will be available to you

at a later time.

DR. DRESLER: And also to that point, to reiterate what was said yesterday, if you want a copy of the slides, you need to e-mail the workshop e-mail and say could I please have a copy of the slides, and then they will be sent to you.

Okay. So our Session 5, the first one for this morning, is Human Factors and Labeling. And the first presenter is James Cheng speaking on General Principles of Human Factors in Product Design.

CAPT CHENG: Hello, can you hear me?

DR. DRESLER: And we're speaking online. Thank you.

CAPT CHENG: Hi. So good morning. I'm Captain James Cheng. I am a senior engineer in the Division of Product Science in the Office of Science, and this presentation will provide a brief overview of the principles of human factors and how they are applied to product design.

Slide, please.

Topics that will be covered are as follows: We will discuss how human factors are defined. We will provide a brief description of the basic concepts and processes. We will provide common tasks involved with human factors. We will discuss how human factors is applied to product development.

We will discuss some standards and references that you may find useful. And finally, we will provide some takeaway concepts.

Slide, please.

This section will present several examples of how human factors are defined by different organizations.

Slide.

The first example comes from the Human Factors and Ergonomic Society. "Human factors is concerned with the application of what we know about people, their abilities, characteristics, and limitations to the design of equipment they use, environments in which they function, and jobs they perform."

Slide.

The next definition is from the Transportation Research Board. "Human factors is the scientific discipline that studies how people interact with devices, products, and systems. It is an applied field where behavioral science, engineering, and other disciplines come together to develop the principles that help assure that devices and systems are usable by the people who are meant to use them."

Slide.

The final example is from the FDA Center for Devices and

Radiological Health, from the CDRH human factors final guidance. "Human factors is the study of how people use technology. It involves the interaction of human abilities, expectations, and limitations with work environments and system design. The term 'human factors engineering' refers to the application of human factors principles to the design of devices and systems. It is often interchanged with the terms 'human engineering,' 'usability engineering,' or 'ergonomics.'"

Slide.

So the general theme outlined by these definitions is that human factors involves focusing on people and their characteristics when designing objects, equipment, or environments that people interact with, taking into account their abilities and limitations, how they perceive information and how they behave. And there are many more definitions of human factors out there.

Some examples, like the CDRH definition as well as many others, equate human factors with ergonomics, while other definitions describe ergonomics as a sub-area of human factors that is primarily concerned with design focused on human anatomy and physical characteristics and physiologic performance or efficiency.

Slide.

So what are the basic concepts involved with human factors?

Slide.

Human factors is a large multidisciplinary field that addresses how people sense and perceive information and their environment, how they process that information, how they behave under differing situations, and how they communicate, as well as the capabilities and limitations of their anatomy and physiology, how people differ in things like height, weight, reach, range of motion, as well as potential disabilities in vision, hearing, and physical limitations. Common disciplines involved in human factors include psychology, engineering, industrial design, and anthropology, and many other disciplines and sub-disciplines, basically anything involved with designing and creating objects and environments that people interact with.

Slide.

A very simple concept is that the use environment, the user, and the product-user interface, which is how a user controls or interacts with a particular object or product, can lead to either a correct use or can potentially lead to an

increase in unintended risks or hazards. So when using human factors, the use environment, user, and user interface are taken into account when designing a product to maximize the likelihood of correct use, while minimizing the potential for unintended risk from a product or environment of use.

Slide.

Now we will briefly describe some of the most common tasks that are performed when applying human factors to product design.

Slide.

Many of you are probably familiar with risk management, and risk management is a central concept to human factors. What makes human factors different are the many different aspects of user and product interaction that are addressed through the use of risk management.

Human factors looks not just at how a product is supposed to work or function, but it also looks at the product from the user's perspective, how hazards may arise from the user trying to use and engage with the product, how instructions for use may be misinterpreted or not be read or possibly that the instructions may not be easily understandable.

And this is where all of these different types of

disciplines are involved in human factors to understand how people behave under normal as well as stressful conditions, and how stress can impair cognitive functions. For example, fire extinguishers are typically used under very stressful conditions and have to be designed for simple operation and straightforward functionality.

So these are some typical tasks and steps or phases involved in risk management. Risk management identifies the product-related hazards, which may include physical, mechanical, thermal, electrical, and chemical aspects. It also identifies use-related hazards involving the user interface design and the use environment, as well as unanticipated methods of use or even inappropriate use. Risk management identifies and categorizes critical tasks and operations. It develops risk mitigation and control measures and strategies. And it also conducts human factors validation testing.

It's important to note that human factors validation testing is often conducted to see if the assumptions about how the product can be used are accurate and complete, and this is often where unanticipated risks or hazards may be discovered that were not foreseen during the design phase.

Slide.

And this is a typical process flowchart for risk management that is taken from the CDRH guidance on human factors. Now, even though CDRH is concerned with medical device safety, the basic principles of human factors outlined here are very general and are applicable to any type of product development.

One key problem with this flowchart is that the process ends once you've documented the process. The process should actually be continuous and reevaluate potential hazards during the life cycle of the product as more information is gained about how the product is actually being used.

Slide.

Here are some important general concepts involved with risk management of various products. Risk management mitigates and controls risk by designing to eliminate or reduce known hazards. Unanticipated hazards are determined through preliminary user evaluation testing as well as through postmarket reports. And most importantly, risk management is a continuous process that does not end with product marketing. It's a continuous life cycle process that keeps going until the product is decommissioned.

Slide.

Now, how can human factors be applied to product design and development?

Slide.

As you may have heard in news reports, the lithium-ion batteries that are typically used in ENDS products can fail and fail catastrophically, not just in ENDS products but in other consumer products like hoverboards, laptop computers, and cell phones.

Now, cell phones and laptops early adopted the lithium battery technology when it was first introduced many decades ago, and they also experienced battery fires and explosions. The industry responded by implementing battery quality control processes as well as battery safety circuitry to minimize risk of thermal runaway. This was often referred to as smart battery technology, and it was widely adopted by the industry.

Recently, however, there has been an increase in reports of cell phone fires and explosions, such as two separate reports of iPhone 6 Plus devices catching fire. So what's changed? Well, cell phones have become thinner and larger, and this has led to some loss of structural rigidity and compression and flexion resistance in the phone.

There have been multiple reports of late model iPhones

losing touch functionality, commonly referred to as touch disease, where the chip responsible for processing touch input experiences mechanical damage from repeated compressive forces during normal use. Now, apparently the solder holding the chip to the circuit board cracks, and the chip loses electrical continuity.

So the lack of sufficient structural rigidity also leaves the battery vulnerable to mechanical damage and consequent thermal runaway. In the two iPhone fires mentioned above, one was subsequent to the user tripping and falling with the phone catching fire in his pants pocket, and the other occurred when the user sat down and crashed with the phone in his back pocket.

Now, another well-publicized battery failure has been occurring in brand new Samsung Note 7 phones, with the news reporting at least 30 cases of the phone exploding or catching fire, in one instance purportedly destroying a car that the phone was charging inside. There hasn't been a lot of publicly released information regarding the specific cause or causes for these failures, but from what little has been provided in public, it may be a case of a design or manufacturing flaw in the battery or perhaps a combination of conditions that may

cause the phone charging circuitry to not properly sense when the phone is fully charged, which can lead to overcharging and eventual damage to the battery electrodes. That then leads to a short circuit or even a mechanical breach of battery containment and subsequent thermal runaway failure.

So, again, risk management is a life cycle process that needs to be continually reevaluated during the product lifespan as well as during product evolution.

This slide lists some of those reported issues involving ENDS products: fire and explosion from the lithium battery and charger; poisoning risk from spills and exposure to e-liquids as well as child safety issues with e-liquid packaging; toxins in the aerosol from contaminants in the e-liquid as well as product emissions where metal nanoparticles and harmful and potentially harmful chemicals have been detected in some aerosols, according to research literature.

Slide.

Now, what are some possible design mitigations and controls for these types of hazards? For fire and explosion risk, other industries have implemented lithium battery quality acceptance testing. Another common mitigation is the incorporation of safety circuitry in the charger and charging

port design to prevent charging with charges that do not meet required electrical specifications. For poisoning risk, tamper-evident and child-safe packaging design and testing is a very common mitigation in other industries. For toxins in aerosols, quality acceptance testing can help ensure purity, and heating element design and temperature control may be able to help mitigate the generation of metal nanoparticles and HPHCs.

Slide.

Under possible mitigations and controls, product labeling is not generally considered the most robust method to assess risk as it sometimes places an unreasonable burden on the user. For example, instructions for use that state that only a suitable charger should be used isn't very robust as most consumers would have difficulty finding and evaluating that information. A more typical design mitigation would be the incorporation of safety circuitry so that the product does not charge when the charger voltage and current are not appropriate.

Slide.

These are some standards and references for human factors that you may find useful. Again, these documents may be

targeted towards certain products or industries, but the principles of human factors that are discussed are applicable to product development in general, although certain processes that are discussed may or may not be applicable to your particular product.

Slide.

Now, this is the AAMI/ANSI HE75 standard that discusses general principles of risk management and usability testing as well as design elements such as controls and software. Although again targeted to medical devices, the general principles are applicable to general consumer products.

Slide.

The next reference is the ANSI/AAMI/IEC 62366 standard that discusses the usability engineering process, again still applicable to general product design.

Slide.

And we also have the CDRH human factors final guidance, which provides a high-level overview of human factors that can also be applied to general product development.

Slide.

And lastly, we also have the HFES 300 guidelines for using anthropometric data in product design, from the Human Factors

and Ergonomics Society.

Slide.

So what are some general takeaways?

Slide.

Generally, human factors involves a multidisciplinary approach. Human factors is a process to design products that people can use correctly. Risk management is an important tool for determining and controlling unintended hazards, and risk management is a continuous process that includes postmarket monitoring for unanticipated user injuries or harm.

Slide.

Now, I'm also a member of the CTP working group on Tobacco Product Master Files, and I wanted to reiterate, as was stated in other presentations, that the Tobacco Product Master Files can be provided to FDA by component manufacturers in support of a tobacco product marketing or clinical research application.

Again, as has been stated in previous presentations, TPMFs allow trade secret and confidential information to be provided only to FDA. TPMF contents are kept confidential from referencing applications. And if you're interested, any additional information on TPMFs can be found at this link on the FDA website that discusses TPMFs.

Slide.

So that's the conclusion of my presentation. Thank you for your time and attention.

DR. DRESLER: Thank you, James.

Our next presenter will be speaking on Label Comprehension, Dr. Priscilla Callahan-Lyon from the Division of Individual Health Science.

DR. CALLAHAN-LYON: Good morning. I'm going to discuss label comprehension. I'm Priscilla Callahan. I'm the Deputy Division Director for the Division of Individual Health Science.

So during the course of this talk, I'm going to give you some background and definitions. I'm going to discuss some general design concepts for label comprehension studies, how to plan and conduct a label comprehension study, a brief discussion of some of the other study types, and the analysis of label comprehension study data.

So Section 910(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, or the FD&C Act, states that a PMTA must include specimens of proposed labeling for the new tobacco product. And 201(m) of the FD&C Act defines labeling as all labels or other written, printed, or graphic material upon any article or

any of its containers or wrappers, and accompanying such article. This includes labels, onserts, inserts, instructions, and any other accompanying materials. So this means that a PMTA must include a sampling of the proposed label for the new product, including any accompanying materials.

In the FD&C Act, it also requires FDA to deny a PMTA and issue an order that the product may not be introduced into interstate commerce if FDA finds that the proposed labeling is false or misleading.

The draft guidance on applications for premarket review of new tobacco products, which is available for comment, states that applicants should address the attractiveness of the product and the product labeling to current tobacco users and to never users and former users. It also states that studies in adult subjects should provide an evaluation of consumer perceptions, including risk perception based on the product itself, as well as packaging and labeling. In the draft guidance there are some suggested ways for evaluating consumer reaction and perceptions of the proposed labeling.

The draft guidance on PMTA for ENDS, also available for comment, states that the submitted specimens of proposed labeling for all product panels should reflect the actual size

and color for use with the new tobacco product, and this should be included as part of the PMTA. FDA recommends that the product labeling include text or graphic elements that would minimize the risk associated with use of the product and text or graphic elements to identify the product. And the text or graphic elements to minimize risks should be directed at both users and nonusers of the tobacco product and should include directions for use, storage, and recharging, if applicable.

Additionally, as noted in the draft PMTA ENDS guidance, warning statements are an important part of the product's labeling. The draft guidance recommends finished ENDS that contain nicotine should include a nicotine exposure warning, and the draft guidance provides an example of the type of warning statement.

The draft guidance on PMTA for ENDS, which is available for comment, includes a statement that the PMTA should provide data that adequately characterizes that the marketing of a new tobacco product would be appropriate for the protection of public health, and that consumer product perception evaluations are an important consideration for this APPH designation. FDA recommends you include studies demonstrating that the users and nonusers understand the product labeling, the instructions, and

that they will use the product according to the labeled instructions.

Now, there is precedence throughout FDA for this type of evaluation. In 2006, the FDA Nonprescription Drug Advisory Committee considered issues related to consumer studies of nonprescription drugs or over-the-counter products. And in 2010, the Center for Drug Evaluation and Research, or CDER, issued a final guidance on label comprehension studies for nonprescription drug products. In 2013, CDER released a final guidance on self-selection studies also geared towards nonprescription drug products. And in 2016, as Dr. Cheng just mentioned, there is the CDRH, or Center for Devices and Radiological Health, guidance on Applying Human Factors and Usability Engineering to Medical Devices.

Now, it's important to note that these guidance documents were not developed for tobacco products, and some of the recommendations and the language do not apply to tobacco products. However, they may provide some useful information for applicants that are trying to design the studies, and I've included here the links to these final guidances.

So some basic definitions. A label comprehension study. This evaluates whether consumers understand the key label

message. A self-selection study evaluates which products consumers choose in a specific circumstance. The actual use study evaluates whether consumers use the product according to the labeled direction. And as Dr. Cheng mentioned, human factors studies evaluate how consumers interact with the product.

I'm now going to discuss some general design concepts for label comprehension studies. The most important thing is -- the first thing that you need to determine is what is going to be the information that you are testing, your primary communication objective.

A study design should be developed that meets the objectives and is appropriately sized to meet the objectives. These are open-label, uncontrolled studies. Preliminary research and pilot testing with different label prototypes might be needed before developing and conducting the larger study. Label development is almost always an iterative process. The appropriate population needs to be considered. The population might need to consider demographics, vulnerable populations, literacy. And the questionnaire that targets the established objectives needs to be developed. It is possible that more than one objective may be tested in a single study,

but you may not be able to test all objectives in a single study.

A priori target thresholds should be established. One correct answer or more than one correct answer, it doesn't matter, but the correct answer for each question should be established, and a target should be established for each communication objective. Test labeling as close as possible to the final labeling should be set.

And when I say target threshold, what I mean is you designate what you consider to be the appropriate number of correct answers. So setting a target of 80% would mean 80% of those questions would get the correct answer. The target threshold can vary from question to question, but there should be a rationale for the levels selected for each communication objective.

So planning and conducting the study: The communication is always the primary objective. It is important to assess the content, accessibility, and comprehensibility of the communication. The product type will be important for determining the specific communication objectives and evaluate whether consumers understand the relevant warning statements, the precautions, and the product ingredients. Consider the

population that is being evaluated. Generally, the sample is broad, but over-recruitment of certain groups might be appropriate.

Labels should be easily understood. For over-the-counter or nonprescription drugs, this is generally set to the fourth or fifth grade reading level. Questions are designed to assess the communication objectives, and they should be direct, specific, and unambiguous. Each question should focus on a single item, and correct or incorrect answers to closed-ended questions should be pre-specified. Pretesting the questionnaire with a sample of respondents may indicate whether the wording of the questions is clear to the subjects.

Different question types can be used: open-ended, closed-ended, multiple choice. So an example of a closed-ended question: Sally is pregnant and would like to take Drug X. According to the label, is it okay for Sally to take Drug X? And the question would have a yes or no answer. An open-ended question could be a follow-up to the same question after they respond to the first one: Why did you say that? And then you would record the open-ended answer. These questions can provide insight of what consumers are thinking and might provide insight for better wording on package labels.

Scenario questions can be used to assess the ability to make decisions based on the label information. And avoiding bias and leading questions is important. Including "I don't know" as an answer is acceptable because it discourages guessing. There are additional examples of questions in the CDER final guidance, and while written for drugs, the basic concepts might be useful for developing the questionnaires.

In terms of logistics, the verification for a complete and accurate recording of the study data should be included in the protocol. Questions may begin with "According to the label," but participants should not be prompted overly throughout the test to look at the label. The questionnaire can be self-administered, or it can be conducted by a trained interviewer. And the optimal location for where to conduct the study needs to be considered, such as a mall or an online survey or some other type of site. Study personnel should be adequately trained, and they should follow the protocol procedures and use scripted queries and responses. And participants should receive adequate training on the study content and format and be given plenty of time to complete the study.

I'm going to discuss briefly some other study types. A self-selection study refers to the decision a consumer makes

about using the product based on reading the information on the label. This can be a separate study or as part of an actual use-type study. And there's more information on this in CDER's guidance on "Self-Selection Studies for Nonprescription Drug Products." And as I stated, these are geared towards drug products, not towards tobacco, but the design concepts are similar.

An actual use study: CDER uses these for over-the-counter or nonprescription drug products, and the focus is on how consumers actually use the product, that is, whether they follow the label or the directions. These are generally naturalistic studies of a product use, typically observational, and the data collection relies on diary methods. And again, these are geared towards drugs, not towards tobacco products, but the basic concepts are the same.

Human factors studies have been discussed in detail. To summarize how consumers interact with the product, whether or not that they can demonstrate their ability to assemble or use the product or the device based on instructions. This can be an iterative process similar to label comprehension studies aimed at improving the device, the instructions, or both. And there's more information in the CDRH guidance or in some of the

other guidances that were previously mentioned.

Analysis of label comprehension studies: These are some general principles on conducting an analysis of the study results. Most importantly, the study protocol should pre-specify the primary endpoints, and this should directly relate to the primary communication objective. The study population should be large enough to provide a reliable answer to the primary communication objective, and any subpopulation that's being evaluated also needs to be large enough to provide reliable information.

Principal features of the analysis plan should be defined in the protocol, such as the statistical methods for characterizing the study subjects, how to define success and failure criteria, and the methods for handling any missing data. A comprehensive statistical analysis plan should be included in the protocol.

And in terms of the final study report, these are some general principles for writing the final study report: the study design and conduct should be included in detail; the recruitment strategy and the response rate, including the full population and any subpopulations; a presentation of the demographics of the study participants; and a detailed

interpretation of study results, including results for the appropriate subpopulations.

I've once again included the links for the final guidances that are available. And as noted, these will be on the slides, and also, I believe, they're on the list that's outside the door.

And I thank you for your attention.

(Applause.)

DR. DRESLER: James, I have your name tag up here, so we know that you're on the line. And Caryn, James is on the line, right, if we have any questions.

Okay. So as per yesterday, please write any questions. Raise your hand if you want a white card, and write your questions down, and then we'll get those reviewed to come up here.

The other thing, too, I saw -- you know, if you want to take pictures, no, those slides are available. So if you just e-mail -- you can take pictures, you're welcome to, or just e-mail the site, and you can get a copy of the slides in PDF form, okay, to get those. And then again, as Priscilla said, that the links are outside, so you can pick those up at the break.

All right, let me start out with one question that we received through the web earlier. Are e-liquids required to have batch numbers and expiration dates on the label?

Priscilla, that's probably for you.

DR. CALLAHAN-LYON: Well, at this point, there's no requirements of any kind, but eventually there will probably be a need for registration, and the batch numbers and the unique ID would be part of labeling.

DR. DRESLER: Okay, so no requirements at the present time, but that's a reasonable thing to do?

DR. CALLAHAN-LYON: Yes.

DR. DRESLER: No questions? I mean, they were good presentations, you guys. Those were very good presentations.

(Pause.)

DR. DRESLER: So there are several cards being collected. So if you are online, I believe the camera is focused just on the front, so you can't see what's going on in the room, but there are cards being picked up. Thank you.

Okay, this is about self-selection studies. While the rationale for such studies is clear for nonprescription medicines, it is not clear why they're necessary for ENDS products.

DR. CALLAHAN-LYON: I'm sorry if I meant to imply that. I didn't imply that they were absolutely necessary. I was just describing them as a type of study that could be considered. And I think it's up to you to determine what you think is appropriate for your product and submit it to us. They are not a requirement.

DR. DRESLER: There's a second part of that question. So what's the goal of conducting them, self-selection studies?

DR. CALLAHAN-LYON: Well, as I mentioned, the self-selection study is to make sure that people can read and understand and appropriately select the product for them. In the over-the-counter world, that's very realistic. It may not necessarily be the best study for an ENDS product.

DR. DRESLER: So this is another question there that follows on this. How would self-selection be conducted? Must this include selection versus a competitive product?

DR. CALLAHAN-LYON: It must not. I mean, there's no "must" in this at this point. Okay, so there's no requirements on how it would it be conducted. That would be up to you. You could design the study however you think would be best suited for your application. It may not be that this is the best test to do. The focus of this was really label comprehension, and I

included self-selection just because that's another type of study that can be done for consumer evaluation, but it is not required.

DR. DRESLER: Okay. I'm going to stay on self-selection studies, okay? So for self-selection studies, are actual physical samples required? For example, cigarettes or e-cigarettes or NRTs, nicotine replacement products, are they required in that self-selection study?

DR. CALLAHAN-LYON: Okay. As I've stated, self-selection studies are not required. The design of the study is going to be up to you to determine how you think is best to design it for your particular product and application. There's no particular requirements for self-selection studies to even be conducted, and the design of it would be up to the applicant.

DR. DRESLER: Okay. So the FDA has mentioned -- and this was pretty much yesterday. The FDA has mentioned that the snus PMTA often is the full and complete application available anywhere, the one where the company has blended their proprietary -- blinded, I'm sorry. Legible helps. Thank you -- the one where the company has blinded the proprietary information.

And so actually, since this one isn't so much for the

presentation that was here and -- so no, the full application is not available, but you could submit a FOIA request. So that's a Freedom of Information Act. And then you would be able to get the information that is not redacted that is commercially confidential information.

So another question: How does the Agency recommend fulfilling labeling requirements of percent domestic and percent foreign tobacco for ENDS products that contain any nicotine? So how does the Agency recommend fulfilling the labeling requirements of the percent of domestic or the percent of foreign tobacco for ENDS products that contain only nicotine?

And so I can answer that one. There's no requirements for that. Again, one of the things we've been emphasizing through this, as you've been hearing, these are draft guidances that are open for comment. So if you have any comments for them, please make them. But at the present time, the reason for the seminar is providing information and helpful guidance as you try and put your applications in for review.

Any other questions? One more is coming from online. Okay. Any others? And also, you know, if a question comes up during the break as you're thinking about it, go ahead and

submit it. We can answer the questions as we go through the other sessions.

Okay. So for short-term and long-term studies, which is from yesterday's health risk talk, clarify time durations of short and long term. Is 5 days sufficient for short term, is 1 to 3 months for long term given that switching biomarkers of potential harm change in 1 month?

So, Dr. Callahan, this is not one that you were presenting on yesterday. Do you want to go for those or --

DR. CALLAHAN-LYON: Sure. Okay, so for short- and long-term studies, I think that's going to be up to the design and the biomarkers that you are measuring. And all that we would ask is that when you submit your application, or if you come in and talk to us in a meeting prior to submitting your application, that you have a rationale for the design and why you think that this would be the best design that would give you the information that you need to support your application.

DR. DRESLER: Okay. Here's another one that's not so much from today, which like I said is perfectly good. If a manufacturer demonstrates, through in vitro data, that flavor variants of a product with the same nicotine concentration has no toxicological concerns based on in vitro studies, would FDA

require separate human studies, short term or long term, for each flavor variant? So, again, as soon as you hear that "required" word --

DR. CALLAHAN-LYON: Yeah.

DR. DRESLER: -- that answer is going to be no, there's no requirements.

DR. CALLAHAN-LYON: There are no requirements.

DR. DRESLER: Okay. Again, make your case.

DR. CALLAHAN-LYON: Yeah, that would be a case where you submit the data, and you can make your case and your rationale, and it would be reviewed.

DR. DRESLER: So for an actual use study, how many participants are suitable? Can we assume less than 100 people?

DR. CALLAHAN-LYON: I don't know that you can assume anything. That would be another situation, in terms of actual use, where you would want to propose your study design and provide a rationale for why you think that that would be the most appropriate study. Actual use studies are not -- they were another study that I included for completion, as much as anything. I'm not necessarily advocating. And as we've stated repeatedly, there are no requirements for actual use studies.

DR. DRESLER: Can I ask you a follow-up question, perhaps

to put you on the spot? Are actual use studies usually more than 100 people?

DR. CALLAHAN-LYON: It depends on what you're testing. In the over-the-counter world, I've seen very small or very large. It depends on the population that's at risk and what you're concerned about.

DR. DRESLER: So that goes to designing the trial up front and studying those priorities up front --

DR. CALLAHAN-LYON: That's your communication objective, and design the study to meet the objective and select the population as needed.

DR. DRESLER: Okay. And I think that's it for the questions, yes? Is that correct, no more questions back there? Okay. All right, very good. Thank you.

Thank you, James, for staying on the line and working through our great technology this morning. So that's excellent. And thank you, Dr. Callahan.

So we'll move on to the next session.

(Applause.)

DR. DRESLER: So the next session is about Initiation, Cessation, and Consumer Perception studies, and our first presenter will be Dr. Chad Reissig, who is the Addiction Branch

Chief for the Abuse -- and he will be speaking on Abuse Liability Assessment and Addiction.

DR. REISSIG: All right. Good morning, everyone. Thank you. My name is Chad Reissig, and I'm the Addiction Branch Chief in the Office of Science, Center for Tobacco Products at FDA, and today I want to talk to you about abuse liability assessment and addiction.

Here's the overview for the presentation. I'm going to talk a little bit about what addiction is and how it's measured. Then I'll discuss traditional abuse liability assessment procedures, including the methodologies that are used, participant recruitment, screening, and other study procedures. I'll talk about dose selection and the types of outcome measures that are used in these studies. And then I'll talk about abuse liability evaluation of tobacco products, including discussion of potential study design parameters, additional outcome measures that can be included in these studies, and the limitations of these study procedures.

So, first, what is addiction? It has a variety of definitions depending upon the source that you're looking at. So addiction has been described as a state characterized by compulsive engagement in rewarding stimuli, despite adverse

consequences. That's the Wikipedia definition.

The National Institute on Drug Abuse says that "Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences."

The Substance Abuse and Mental Health Services Administration says that "Substance use disorders occur when the recurrent use of alcohol and/or drugs causes clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home."

And so you can see that these definitions are relatively varied, but I've underlined some of the common components across all of them, including compulsive engagement in use, use despite adverse consequences, and the use generally results in clinically significant impairment.

So how do we measure addiction? Well, unfortunately there are no biomarkers or single outcome measures to diagnose or measure addiction. In fact, clinical diagnoses and outcome measures of addiction are generally qualitative in nature, such as what we might see in the Diagnostic and Statistical Manual of Mental Disorders, the Fifth Edition, where diagnosed tobacco

use disorder is generally based on qualitative criteria.

However, like the definitions, these measures of addiction generally manifest as an inability to quit, craving, a withdrawal syndrome upon drug discontinuation, and clinical impairment, which is sometimes referred to as use despite harm.

Despite the difficulties in defining and measuring addiction, research methodologies to predict and infer the abuse liability of substances have been proposed, and I'm going to talk about those.

And so I want to shift gears to talk about traditional abuse liability assessment, and traditional abuse liability assessments are designed to evaluate the likelihood of abuse of a drug, but they can also assess the consequences of abuse. So there are two things here. We can get a sense of how likely someone will use a drug and then the consequences of that use or what happens if and when they do abuse or misuse a drug. And these methodologies have been used to evaluate pharmaceutical drugs, including opioids and stimulants, but they've also been used to evaluate nicotine-based drugs as well, such as nicotine replacement therapies.

And these regulatory procedures for abuse liability assessment, they've been described as early as the 1990s, and

they have evolved since. However, abuse liability assessments for tobacco products, they're actually less well developed. So I want to talk about these methodologies.

The current gold standard for clinical abuse liability testing and potential drugs of abuse involves a placebo-controlled, multi-arm study. In these studies, quite often an experimental drug or a new drug is compared to a positive control comparator and placebo.

In these studies, peak ratings of drug "liking" are typically the primary outcome measure, and these are assessed using a visual analog scale, or VAS. And I'll talk about these a little bit later in the presentation. In addition to the VAS measurements, additional outcome measures are also included, and these can include psychomotor assessments or measures of hand-eye coordination and additional outcome measures.

In traditional abuse liability assessment, study participants typically include individuals with prior experience using similar drugs, and this is thought to increase the sensitivity of the study. For example, experienced drug users are often better qualified to describe and evaluate the subjective effects of drugs of abuse. Since these individuals typically use these drugs, it's thought that they are probably

the best population to assess their effects. In addition, in these traditional abuse liability studies, drug-naive participants can find study drugs aversive. This is especially so at higher doses and/or recreational doses.

The recruitment for these studies usually employs standard recruitment methodologies, such as newspaper, magazine, and media advertisements. But they can also include things such as snowball sampling and refer-a-friend recruiting incentives. And in these procedures, once a subject is enrolled in a study, they can then refer or talk to their colleagues or friends in order to get them enrolled and participate in the study. And using this method, one participant finds another one, and it begins to snowball as more participants enter the study.

After recruitment, participants typically undergo basic screening procedures to determine their study eligibility, and this usually includes a medical examination. And typically, participants are generally healthy, with significant medical conditions being excluded. So other than liking and using recreational drugs, usually these participants are otherwise healthy.

In these studies, a qualification or a prescreening session may be employed, and this usually involves

administration of a placebo and an intermediate dose of the positive control in a pre-session. So what happens is after volunteers are screened, on one day they may receive a dose of a positive control and they're asked if they like it, and then in an alternative session they receive a placebo. In using this prescreening procedure, we can help ensure that participants unequivocally like the positive control, but we can also help control for placebo response. So if individuals rate the placebo as being liked very much, we can design the study so that those individuals do not go on in the study.

Traditional abuse liability assessments have relatively standard study procedures, and usually they're double-blind, double-dummy, and they have within-subject design. So the double-blind nature means that neither the participant nor the researcher knows what drug is being administered on any day, and the double-dummy design can be used to further enhance blinding of the study, if it's required.

For example, if we have a particular drug that has a really strong taste, when we administer that to a subject, they're going to be able to taste it, and they will be able to break the blind and determine that they received the drug. So in that case, what we could do is we could match the placebo

and the positive control by giving it a really strong taste so that when the drugs are administered, they both elicit a strong taste and the subjects can't tell the difference between the two.

And the within-subject design simply means that each subject can serve as their own control because they receive every dose in the study.

And during study sessions, ratings of drug "liking" and other effects are usually assessed repeatedly after drug administration using a visual analog scale, as I mentioned before. And in these studies, peak ratings of "liking" are usually the primary outcome measure. Psychomotor measures, like hand-eye coordination or cognitive effects, can also be employed to gather information on the consequences of abuse of the new drug.

And in these studies, the abuse liability of the test drug is then assessed by comparing its effects with those of placebo and also the positive control. And in these studies, doses typically include supra-therapeutic doses of the test drug, and that is, these are doses above and beyond the therapeutic dose.

And so I want to talk about dose selection in the traditional abuse liability study. So in these studies, dose

selection is usually justified, and in the study, multiple doses of the new drug and a positive control, a single dose of the positive control, are typically assessed to determine location on the dose-response curve, and usually we test at least three doses of the new drug. And the cartoon below helps explain why.

So on the x-axis here we have the dose of the drug, and on the y-axis we have "liking," and we can see that as we begin to increase the dose of the drug, in general, we get an increase in "liking." However, if we increase the dose too high beyond a particular point, "liking" begins to decrease, and this is thought to occur because the dose is too high. So at these higher doses, we're beginning to elicit potential adverse effects or toxicity, and that can help decrease "liking" scores. And so this is why we use three doses, because it helps us determine where along this curve the doses of the new test drug are.

Here's an image of the inside of a typical abuse liability laboratory. What you see here are chairs for the study participants to sit in, and then the computer here is where they complete the visual analog scale assessments and other outcome measures.

Here are some images of a human abuse liability laboratory that has been adapted for study of combusted products or products that elicit some type of aerosolization. And you can see it looks almost identical to the previous slide where there's a chair and subjects can fill out their assessments on the computers here. But notice that there are these ventilation ducts here, and in this way we can have subjects use or smoke a particular product, and it can be ventilated.

What I want to show you with this next image is that these types of studies can be done in a single-person session, and they can also be done in a group setting as well.

So here are some examples of outcome measures. And this is an example of the visual analog scale assessments that I mentioned previously. So when a subject is seated in front of those computers, typically the computer will present them with a question, and in this case the question is "Do you like the drug effect?" And below the question is a line. Typically, it's about 100 mm, and you can see that the line is anchored on opposite ends with opposite phraseology such as "No, not at all" and "Yes, very much." And once a subject is administered a drug, they are then asked to rate their "liking" by placing a mark anywhere along this line, and these are typically done

repeatedly after drug administration.

And this is what it looks like. So what you're seeing here are some examples of drug "liking," and you're looking at the time course in peak visual analog scale "liking" scores. These are data adapted from Reissig and Griffiths in their data examining alprazolam, an oral sedative.

Starting with the left-hand panel, on the x-axis here we have time, and this is time after drug administration, and on the y-axis we have the participant rating. And in this case, the rating is on a 0 through 4 scale, but it's a similar visual analog scale as I just showed you.

In the inset here we can see the dose conditions. They include placebo and increasing doses of alprazolam, and what you want to observe is that after administration of placebo, we get a very low-level response in "liking," and this is what we would expect. There's not an active drug, and so we wouldn't expect subjects to like it.

However, as we increase the dose of the drug, we see a nice dose-related increase in ratings of "liking." In addition, you can see that the time course of these "liking" effects, the time course occurs with absorption of the drug. So drug is administered. It is then absorbed into the

bloodstream, and as it's absorbed, it coincides with the peak "liking" scores.

On the right-hand figure, here you're looking at the same data, except in this case we're looking at the peak effect. So as a subject rates their "liking" during the course of the study, the maximum effect is the peak effect, and that's displayed here.

So in this graph, instead of time on the x-axis, we have dose. So we have the placebo and then the increasing doses of alprazolam, the same visual analog scale on the y-axis. And we can see once again that the placebo elicits a relatively low "liking" score and then this nice dose-related increase as we increase the dose of the drug.

Traditional abuse liability testing has, in fact, been used to examine nicotine-containing products and NRT. Here we see some more data for -- in an examination of the subjective effects of nicotine lozenge. And like the previous graph, on the x-axis we have the dose condition for the nicotine lozenge, the gum, and the positive control comparator, amphetamine. And on the y-axis we have the visual analog scale score, which is indeed on a 100 mm scale.

So what we see here is that when given a placebo, subjects

once again demonstrate relatively low levels of "liking." But for the nicotine lozenge, we have a relatively flat dose-response curve. And, in fact, it's very similar to the 4 mg of nicotine gum. And by way of contrast, when we look at a drug with known abuse potential, such as amphetamine, we see that the "liking" scores are significantly greater.

And so those are the types of traditional abuse liability assessment procedures that have been used. And although procedures for abuse liability testing of new drugs and pharmaceutical drugs are relatively well established, abuse liability testing procedures for non-drug products, including tobacco, they're less well developed.

However, abuse liability testing of tobacco products may offer data and information to support 910(c) of the Food, Drug, and Cosmetic Act, including an understanding of the increased or decreased likelihood that existing users of tobacco products will stop using such products, and also the increased or decreased likelihood that those who do not use tobacco products will start using them.

And the methods and the procedures of traditional abuse liability study design that I just talked about may be applicable to the study of tobacco products, including

justifying a participant's selection. So, for example, the traditional abuse liability studies assess "liking" in participants that are familiar with the effects of similar drugs. And for tobacco products, we can evaluate abuse liability in multiple populations, including light or heavy tobacco product users, dual users of tobacco products, mentholated tobacco product users, and so on.

In addition, choice of comparator and dose selection is also important. So what doses should be examined, and what are the positive and negative control comparators? For example, is "own brand" the appropriate positive control, and is a negative control needed?

So in addition to the subjective effects assessment, the visual analog scale ratings of "liking," additional outcome measures may be obtained in these studies of tobacco products, including other subjective effects assessments such as urge to use or lightheadedness. And these can help us contextualize the "liking" scores.

So the "liking" just tells us how much somebody likes a particular product, but other subjective effects assessments can help us determine the why. So if someone really likes a particular drug or tobacco product, it could be because of the

taste, flavor, or because of the nicotine content, and we can simply ask those additional questions. So in addition to "liking," we can say do you like the flavor, do you like the throat hit, and things like that.

Topography measures can also be included, and topography measures give us insight into how a participant uses a tobacco product. And traditionally, these have been used to assess the behavior and use of cigarettes. And you can see some cartoons below of topography devices. On the left is the CReSSmicro, and on the right is the desktop version, and these are just examples. There are more models and brands than these, but these are just examples.

And the topography measurements help us determine a variety of use parameters. So once a cigarette is inserted into one of these, we can then determine the number of puffs someone takes off of it. We can determine the inter-puff interval or how much time occurs between puffs. We can determine the amount or volume that they are inhaling and peak flow and peak velocity as well. And those can help us determine use behaviors.

Measures of withdrawal alleviation can also be used, and these are typically performed after overnight abstinence. And

what we can do is we can determine the degree of withdrawal that an individual or participant is in, and then we can determine how use of a tobacco product can affect or decrease that withdrawal.

Clinical pharmacology outcome measures can also be included, such as exposure. And Dr. Schroeder is going to talk about those right after me, so I won't touch on those too much. Nonetheless, the rationale for the selection of each outcome measure and its interpretation are often clearly justified to help assist in data assessment and interpretation.

So given the abuse liability evaluation, there are some additional questions for consideration, such as the translation of traditional abuse liability measures to tobacco. As I mentioned earlier, most of these were developed for assistance in pharmaceutical drug development, and so I've talked about some of the aspects that may be applicable to tobacco products.

When are changes in selected outcome measures clinically meaningful? So, oftentimes with the visual analog scale score of "liking" being the primary outcome measure, we have to determine when a change in those "liking" scores becomes meaningful.

And what are the most important measures of tobacco

product abuse liability? So in addition to "liking," how do the measures of alleviating withdrawal play a role in the evaluation as well?

And finally there are, in fact, some limitations with these traditional abuse liability methodologies. For example, traditional abuse liability studies do not assess marketing, label claims, and/or perceptual effects on users. In fact, traditional studies are usually done double blind, so these elements are completely eliminated, but they're certainly present in tobacco products.

And finally, abuse liability evaluations must be considered within the context of other abuse-related outcome measures, such as time to first use and overall use. And the abuse liability evaluation is only one component that's involved in the overall evaluation, and it's going to be reviewed in conjunction with a lot of the other types of data that we've talked about during this workshop.

So those are some references. And that's the end of my presentation.

(Applause.)

DR. DRESLER: Thank you, Chad.

Our next presenter will be Dr. Megan Schroeder, who is a

lead pharmacologist within our Division of Individual Health Science, and she will be speaking on Clinical Pharmacology to Inform Abuse Liability.

DR. SCHROEDER: Hi, my name is Megan Schroeder, and as Carolyn said, I am a clinical pharmacologist within CTP's Addiction Branch, and today I'll be discussing how clinical pharmacology studies can be used to inform abuse liability.

So first I'll discuss a little bit about why we study abuse liability. Then I'll go into the typical -- how clinical pharmacology has been typically used to inform abuse liability. Then I'll talk about general principles of tobacco product clinical pharmacology studies.

The CDER draft guidance for abuse liability, available for comment, states that abuse liability and abuse potential is defined as all the properties of a drug, including chemical, pharmacological, and pharmacokinetic characteristics. To address these aspects of abuse liability, studies typically involve both behavioral and clinical pharmacology. Behavioral pharmacology is the study of the effects of drugs on behavior, like Dr. Reissig just discussed. But the topic of this presentation is on clinical pharmacology, or the study of drugs in humans. Specifically, clinical pharmacology entails

pharmacokinetics, or how the body affects the drug, and includes drug absorption, distribution, metabolism, and excretion; and pharmacodynamics, or how the drug affects the body.

In this talk, I'll primarily be referring to three clinical pharmacology terms: Cmax, Tmax, and AUC, or area under the curve. Cmax refers to the maximum drug concentration, whereas Tmax is the time at which that maximum concentration occurs. AUC, or area under the concentration versus time curve, is a measure of drug exposure during a given time period.

Here's a graphical representation of these pharmacokinetic terms. So time is here on the x-axis, and drug concentration is on the y-axis. The drug is administered at time zero, and it increases to its peak concentration at a Cmax concentration and a Tmax time. The total area under this curve describes the total exposure to the drug.

Specifically, the CDER draft guidance of abuse potential, available for comment, states that studies should address several clinical pharmacology parameters such as Cmax, Tmax, area under the curve, and bioavailability, or the amount of drug that makes it into the blood. For example, clinical

pharmacology studies of nicotine replacement therapy, or NRT, have investigated several of these pharmacokinetic parameters.

In this paper, Callens and colleagues measured several pharmacokinetic variables in the nicotine lozenge and the nicotine gum. And you can see how the formulation has an apparent effect on the highlighted areas of Cmax, Tmax, and area under the curve.

Specific to nicotine-containing products, reporting of these clinical pharmacology parameters is important to inform the abuse liability of a product because the rate of nicotine absorption influences abuse liability and that the nicotine delivery system dictates nicotine pharmacokinetics. Thus, drugs that deliver nicotine to the body or brain faster may also have a greater abuse liability or abuse potential. Clinical pharmacology studies therefore are able to provide insight into a nicotine product's abuse liability.

Indeed, several clinical pharmacology studies have indicated that the abuse liability of some NRT products may be low in comparison to cigarettes. Although the data shown here were collected under vastly different conditions, in this figure you can see the rapid delivery of nicotine from cigarettes here in the red line, and the relatively slower

delivery from the gum in the blue and the teal lines, the nasal spray, which is in the purple, and the patch, which is this gray line. What's also apparent in this figure is the lower Cmax and that the nicotine exposure is sustained or maintained longer in these latter products compared to cigarettes.

Based on these and similar studies, the FDA-approved drug label for the nicotine nasal spray (Nicotrol NS) states that its dependence potential or abuse liability is higher than NRT and lower than cigarettes. Particularly, these claims can be made based on the nasal spray's speed of onset, or the Tmax, and the plasma nicotine concentrations, or the Cmax, compared to the nicotine gum and patches, which are low abuse liability products, and cigarettes, which are considered to be high abuse liability products.

To specifically address how clinical pharmacology can be used to inform tobacco product abuse liability, I want to highlight a portion of the draft guidance on PMTAs for ENDS, available for comment, that states "Abuse liability evaluations, including pharmacokinetic evaluations, should consider the addictiveness and abuse and misuse potential of the new products and the exposure to nicotine during product use."

Again, it is well known that pharmacokinetic parameters associated with nicotine delivery, such as Tmax and Cmax, may play an important role in the abuse liability of tobacco products.

Importantly, for abuse liability assessments, it is well documented that variable nicotine absorption is based on product type. Specifically, researchers have found that nicotine absorption from inhalation is typically more rapid than dermal or oral mucosal delivery and is therefore an important concept to consider in evaluating the abuse liability of tobacco products.

This figure displays both the rate and extent of nicotine delivery from several tobacco products, including cigarettes, oral snuff, and chewing tobacco. Again, time is on the x-axis here, and blood nicotine concentration is on the y-axis. The Tmax from smoking, where nicotine is absorbed via inhalation, is faster than that from snuff or chewing tobacco, where nicotine is absorbed via oral mucosal delivery.

Now I'll go over some of the design features of tobacco product clinical pharmacology studies. Where applicable, these studies and clinical studies in general tend to be randomized trials with negative or placebo controls. They typically are

crossover studies where a participant will use various product or products and doses on separate days, and therefore the statistical comparisons are done within subject.

Typically, studies to evaluate pharmacokinetics or other parameters of study products are done -- I'm sorry. Typical studies evaluate the pharmacokinetics or other parameters of study products rather than own brand products due to brand loyalty and subjective "liking" scores.

These studies may also evaluate a range of doses or, in the case with ENDS, e-liquids with a range of nicotine concentrations or voltage differences or in ad libitum conditions where participants can use the products as much as they'd like.

And finally, to control for any residual or remaining nicotine from prior use of tobacco products, these studies typically require at least overnight abstinence that is then biochemically confirmed through exhaled carbon monoxide or cotinine, depending on the product.

Unlike most drugs, tobacco products are used ad libitum, not based on any dosage requirements, and therefore many studies typically include both a prescribed use session, where participants use the products in a standardized way, and also

in ad libitum use sessions, where participants can use the products as they'd like.

The prescribed use sessions are similar to the idea of single dose studies in drug clinical studies and are typically used to assess nicotine pharmacokinetic parameters, including Tmax and Cmax. In these studies, researchers typically collect sufficient blood samples to properly evaluate the nicotine concentration versus time profile.

Ad libitum use sessions are used to assess nicotine exposure associated with multiple product use and more typical use behaviors. In these sessions, participants can use the product as they'd like in the laboratory. These sessions are similar to the idea behind multiple dose drug studies. But because duration of abstinence may affect use behaviors, researchers also consider the duration of abstinence before these sessions. Next, I'll show two examples of study designs that incorporate both of these sessions.

This figure is taken from a 2015 Society for Research on Nicotine and Tobacco poster presentation from Dr. Benowitz's lab, where the prescribed use or standardized session, shown here in the blue circle, dictated that participants use the e-cigarette for 15 puffs, 1 every 30 seconds. Then the

participants abstained for 4 hours, during which sufficient blood samples were collected to evaluate nicotine pharmacokinetics.

After this abstinence period, there is a 1.5 hour ad libitum session shown in the red here, where blood is collected less frequently to evaluate the nicotine exposure upon multiple product use and more typical use behaviors.

I should also note here that this study was conducted with participants' own brand, usual brand ENDS products, because the aim of the study was to investigate the clinical pharmacology and nicotine exposure associated with own brand products, not a specific ENDS product.

This next example is from a publication from the Dawkins lab, where study e-cigarettes are used according to a prescribed regimen for 10 puffs, shown in the red box, and shortly thereafter, participants use the product for a 1-hour ad libitum session shown in the green. Throughout, plasma samples are collected to evaluate nicotine pharmacokinetic parameters and nicotine exposure associated with single and multiple product use.

Another type of study design commonly employed to assess tobacco product nicotine exposure under real-world conditions

is an actual use study. In these studies, participants use the study product or own brand product, based on study design, outside of the laboratory, and after some period, less invasive salivary or urinary samples are collected to measure cotinine, the major metabolite of nicotine. This metabolite has a longer half-life than nicotine and is therefore used to assess nicotine exposure over longer periods of time.

These studies typically use between-subject comparisons. Because they are conducted in the real world, researchers often consider compliance with the study and participants' use of other nicotine-containing products that may affect nicotine exposure.

In his study with a population of e-cigarette users, Etter evaluated the nicotine exposure associated with using only e-cigarettes in the past 5 days by measuring salivary cotinine. In this figure, cotinine, the primary nicotine metabolite concentration, is on the x-axis, and how often the study population had these exposures is measured on the y-axis. You can see the wide variability and distribution in cotinine concentrations with e-cigarette use. You can also see in the figure legend that the authors considered the use of other nicotine-containing products in their analyses and focused this

figure on e-cigarette only use in the past 5 days.

Another important aspect of study design is how the study population may affect study results and interpretations. Using ENDS as an example, Farsalinos and others have shown that smokers naive to e-cigarettes use ENDS differently and have lower nicotine exposures than do current experienced e-cigarette users.

In this figure, you can see that the nicotine exposure in smokers, in the red, is much lower than those in vapers or current experienced ENDS users who are experienced and who know how to use the product to adequately get nicotine. Dual use of e-cigarettes and cigarettes may also impact nicotine exposure.

Additionally, how often a person tends to use a product may impact their nicotine exposure in a clinical study since, generally, people who use a product more frequently have a greater nicotine exposure. For ENDS especially, cessation history and the intentions behind using ENDS may also impact study results and interpretations.

Finally, demographics (specifically, gender, age, and ethnicity) have been shown to impact nicotine pharmacokinetics. A participant's nicotine metabolite ratio, or the extent to which nicotine is metabolized into cotinine, may also impact

use behaviors.

These tobacco product clinical pharmacology studies have typically collected biological samples of plasma, urine, and saliva. And they measure several biomarkers of nicotine exposure, including nicotine, cotinine, 3-hydroxycotinine, which is a nicotine metabolite, and total nicotine equivalents, which is the sum of nine or more nicotine metabolites.

Typically, these studies report various clinical pharmacology outcomes, including nicotine bioavailability, Cmax, Tmax, and area under the curve. They also report nicotine pharmacodynamic effects and try to correlate the psychoactive drug effects with plasma concentrations.

In these types of studies, the pharmacodynamic markers typically include vital signs. As previously mentioned, other biomarkers of nicotine exposure have been included in study outcomes, and use behaviors may also be correlated with nicotine pharmacokinetics to understand those relationships.

Typical clinical pharmacology studies often include a comparator product. For example, earlier we saw the pharmacokinetic parameters of the nicotine gum as compared to the nicotine lozenge. Some ENDS studies have utilized a nicotine-free ENDS product as a negative control. Studies with

combusted tobacco products have utilized unlit sham smoking sessions to provide a negative control.

Researchers also consider the influence of nicotine delivery kinetics in studies on abuse liability and choose a comparator product that allows a better interpretation of abuse liability for their study product.

And for the case of ENDS, first-generation ENDS have been shown to deliver less nicotine than second- and third-generation devices, and therefore researchers may choose to use different ENDS products as comparators.

Here I've listed other common principles for tobacco product pharmacology studies. Pharmacodynamic properties, including heart rate and blood pressure, are often collected concurrently with pharmacokinetics to allow comparisons between the nicotine effects on pharmacokinetics and pharmacodynamics.

Switching studies is common too, where participants may be directed to substitute an e-cigarette with similar nicotine delivery for their usual brand cigarette.

As with any scientific study, researchers often justify their selection of a certain prescribed puffing or smoking regimen, and they may also justify the selection of their comparator products, e-liquid nicotine concentrations, and any

use of flavors.

Because the literature has shown that different ENDS products deliver different amounts of nicotine, researchers also identify study limitations, often using the literature to provide sufficient scientific rationale for the bridging between products and studies. Therefore, a discussion of the existing literature is often included in these study rationales and/or publications.

And, in summary, Dr. Reissig and I have provided evidence suggesting that a tobacco product's abuse potential or abuse liability is often determined through multiple lines of evidence, including both behavioral and clinical pharmacological considerations.

However, clinical pharmacology studies alone may not be sufficient to make comprehensive abuse liability conclusions.

Lastly, as for any scientific or clinical study, scientific rationale and justification of protocol details and interpretations is important.

And I have included all the references used in my talk. And thank you.

(Applause.)

DR. DRESLER: Okay, cards please. I don't have questions

from this session that came in online, so we need those cards.

(Pause.)

DR. DRESLER: So this is a message for me to make sure that we are not providing guidance. So basically, as you have heard repeated, I think, with every presentation, that the slides are talking about the draft guidance that is out and it's open for comment. So I was going to reiterate that again and again at the end of the meeting, that you are more than welcome and encouraged to put your comments in for that. But basically, for the information seminar that we're doing, is providing clarifications and general principles, okay? So that is a draft guidance and no requirements.

Okay, ENDS. Given that ENDS products obviously are not drugs, what does FDA see as abuse of an e-cigarette? There is no recommended number of puffs per day, so what kind of amount of use represents abuse?

DR. REISSIG: Yeah, that's a good question. And typically with regard to a drug model, abuse and misuse are much easier to define because there is a prescribed regimen of taking them. So in this case, I think that's a correct statement in that there are challenges to defining both abuse and misuse. So I think we would start with perhaps the more egregious examples

if individuals were using really, really large amounts of e-liquid or had issues where their use of an ENDS interfered with day-to-day function.

DR. DRESLER: Okay, so this question I'm going to start out with, and it says can a PMTA be approved without -- yeah, let me just make it really clear. The Center for Tobacco Products does not approve any product. Marketing authorization, okay? So other parts of the FDA approve drugs, but the Center for Tobacco Products does not approve anything. It is marketing authorization.

So can a PMTA be authorized for marketing without any abuse liability study having been conducted?

DR. REISSIG: Yes.

DR. SCHROEDER: You can use the literature to help you with the scientific justification, study rationale, and linking your products to study products used in the literature.

DR. DRESLER: Okay. Can the abuse liability of a nicotine delivery product be adequately assessed without data on in vivo nicotine pharmacokinetics? So Megan, I was thinking of what your answer just was. Can the abuse liability of a nicotine delivery product be adequately assessed without data on in vivo nicotine pharmacokinetics?

DR. SCHROEDER: I think it can be, but again, use the scientific literature to help support your abuse liability conclusions.

DR. DRESLER: So Chad, or actually both of you, but this is an interesting one. Liking, what is the effect for tobacco products? Does that mean satisfaction?

DR. REISSIG: Yeah, that's a good question. So in the presentation, the visual analog scale that I showed, that's typically quite literally what participants see. And so they are asked do you like use of this product, or what is the effect right now? So whether or not that is synonymous with satisfaction, I think it's -- I think "liking" is a face-valid metric as to how much an individual likes the particular drug, and that could be considered synonymous with satisfaction at times.

DR. DRESLER: Okay. Is the dose curve randomized? So when you're doing that multi-arm study in a single individual, do you randomize the order of giving low, medium, or high? Or do you give it low, medium, high, or some people get high first? Does that make sense?

DR. REISSIG: Typically, it is in abuse liability studies, and the reason is because the studies are conducted double

blind. And so as you could imagine, if somebody came into a laboratory, and the first day they received a very high dose of drug, if that produced any adverse effects, that could produce some amount of carryover where the individual says, you know, the first session I was here was really awful. And so it could influence their future "liking" scores. So yes, oftentimes they're counterbalanced and randomized.

DR. DRESLER: Okay. How is the visual analog scale discretized? And I'm not sure if that's a word, but how can you make a distinction? So, you know, you had the scale up there, and you said there's usually 100 mm. So how do you know that one line that's here is different than one line there?

DR. REISSIG: So generally they're done on the computer and with computer-assisted visual analog scales, it's relatively easy to determine where the lines -- when they are discrete and separate from one another.

DR. DRESLER: So it's usually just a measurement of the length. So it's just 0.7 versus --

DR. REISSIG: Um-hum.

DR. DRESLER: -- 7.2, and so it's a number that the computer then measures.

DR. REISSIG: Yes, it is.

DR. DRESLER: Okay. In the amphetamine example, how do you know the dose was not too high for comparison?

DR. REISSIG: So in that specific example, I would guess that the dose was derived from the literature. So amphetamine is a relatively common comparator in these types of studies, and so it's been used in other abuse liability studies relatively frequently, and so we can derive the dose from those.

DR. DRESLER: When selecting a comparator product specifically for combustible tobacco reference, would you consider the Kentucky reference product appropriate?

DR. REISSIG: I think that's a good question, and the choice of a comparator is tricky. On one hand we might speculate that, compared to own brand, no subject is going to like a novel product as much as they would their own brand. And so in some cases having a reference could produce an advantage in that it's going to be the same product and all the participants are switching out of their own brand to a different positive control.

DR. DRESLER: Okay. Can PK and PD study results from a first- and/or a second-generation ENDS product, could it be used to bridge to a third-generation ENDS product? So if

you're looking at the pharmacokinetics and pharmacodynamics and you did a study in a first- or second-generation product, could those studies be used to bridge to the third-generation product?

DR. SCHROEDER: And just to reiterate what we've said before, that we're not saying that abuse liability studies have to be conducted for any PMTA application. But you could use, you know, scientific literature from first- or second-generation devices to support a PMTA for the third-generation product, but you really need to include your scientific rationale and justification and provide adequate bridging.

DR. DRESLER: Okay, so I'm going to push you on that one a bit because the question wasn't about abuse liability per se, but it was about PK and pharmacodynamics, and you had mentioned during your presentation that the first-generation products didn't deliver nicotine as well. So in PK and PD, so a standard pharmacological study, could you use those as bridging studies for that third generation?

DR. SCHROEDER: So you still probably could again, you know, include rational scientific justification. But then you could also look at the nicotine delivery in nonclinical studies and use that to help in your clinical PK and PD assessments.

DR. DRESLER: Okay. Now I'm going to struggle with this next one because -- you know, I am wearing my glasses, you guys, for my older age so I can read this, but sometimes we all know penmanship can be interesting.

The first one is again with the multiple dose levels administered in what order. And I think, Chad, you addressed that already, that it would be randomized.

Okay, in a PK-based -- I am going to save that one, and I will read through it again as you guys are answering another question.

So, okay, would bridging using PK studies for a representative flavor in a class of flavors be sufficient to represent the class? So would bridging using PK studies for a representative flavor in a class of flavors be sufficient to represent the class?

DR. SCHROEDER: I don't think we're suggesting that you should do these clinical studies on every single flavor. Again, just providing enough rationale and justification for why you're bridging from your specific flavor to other flavors in that category would be helpful.

DR. DRESLER: Okay. I'm sorry, I was trying to read this one. Okay, I think I have it. Is a PK-based argument

sufficient in place of conducting an abuse liability study? In other words, if the nicotine delivery Cmax and AUC is less than a combustion cigarette, is that enough to convince the FDA that an abuse liability study is not needed? So a PK-based argument sufficient in place of conducting an abuse liability study, so if the nicotine delivery is less than a combustion cigarette.

And so again you're alluding to, for example, a first-generation cigarette delivers less than a third-generation cigarette, but it's -- perhaps in this question, it's less than a combusted cigarette. Is that enough to convince the FDA that an abuse liability study is not needed?

DR. REISSIG: So I think the answer is it depends. And so in this case specifically, one of the things we might also consider is the overall use parameters of each of the products. So even if the PK is less than that of a traditional combusted cigarette, we might want to know how -- the difference in use parameters. So is somebody using an ENDS intermittently all day, throughout the day, for 12- to 15-hour periods versus -- and how that might differ from use of combusted cigarettes.

DR. SCHROEDER: And that goes to the importance of these actual use studies and how much they can provide evidence for these types of questions.

DR. DRESLER: It appears from a publicly accessible assessment report on the Swedish Match PMTA that FDA approved those products. Didn't approve. Marketing authorization. So the FDA provided marketing authorization for these products without abuse liability studies. Under what circumstances would a manufacturer be expected to conduct an abuse liability study for an ENDS product as part of their PMTA? So under what circumstances? So it says that the Swedish Match PMTA didn't have any abuse liability studies. So under what circumstances would a manufacturer be expected to do that for an ENDS product?

DR. REISSIG: So unfortunately, I think it is on a case-by-case basis. And to answer this question, I think I would encourage those to actually go back and review what was in that particular PMTA and see the types of data that were submitted and how they were reviewed and interpreted.

DR. DRESLER: Okay. And then this is a clarification. The Kennedy reference cigarettes that were asked before, whether those would be an appropriate comparator. So they're designed for analytical chemical measurements, and they're not recommended for human use. So that might answer that question, maybe. Don't use those as you compare the product.

Dr. Reissig, you mentioned harm as a prerequisite of addiction, so that is, under the definitions you provided of beneficial behaviors, are by definition not addictive. Is harm considered in absolute or relative terms?

DR. REISSIG: Depending on the context, I think it's somewhat of a relative term. If you look at most of the definitions of addiction and abuse, clinical impairment or harm is usually one component, and repeated attempts to abstain or not use a substance are also included in those definitions. So harm is usually just one component of our definitions of abuse and substance dependence.

DR. DRESLER: So is it ethical to do an abuse liability study in a population of vapers, not smokers, with a combustion cigarette arm?

DR. REISSIG: Generally, we would not want to expose individuals that do not use combusted products to combusted products.

DR. DRESLER: And I think if I look at that one, that would presume that these are people who are using ENDS products that started on ENDS and never used cigarettes, is probably where that question is going. So they started de novo on an ENDS cigarette.

Okay. So any other questions?

(No response.)

DR. DRESLER: No? Good. Thank you, those were -- I'm sorry, in the back? No. None online either? There is one coming that's online? Okay. You know, sometimes you think up here I'm taking your time, and I know you're all looking at me, and let me assure you, you don't want to hear me sing. That would be a really, really bad idea.

(Laughter.)

DR. DRESLER: And then, even though I think I can never remember good jokes, and you know it's all in the delivery anyway, so -- and that I'm not good at.

(Off microphone comment.)

DR. DRESLER: No more questions? Okay, very good. All right. So we are doing fast, on time. Well, fast, on time. But that means we have plenty of time for questions. So, please, this is your opportunity to get those questions in. If you think of any that were raised this morning or yesterday during the break, go ahead and write them up.

We will take a 15-minute break, so we'll come back here, we'll say, at 10:30, okay? So we'll start again at 10:30 for our last session.

Thank you.

(Off the record at 10:12 a.m.)

(On the record at 10:30 a.m.)

DR. DRESLER: Okay. So as we're getting back, Dr. Lindsey, you wanted to make some comments before we started on the next session.

DR. LINDSEY: Yes. Good morning, everyone. I just want to take a minute just to remind you about some housekeeping rules here that I had actually mentioned yesterday, but I think, in light of some of the questions that we're getting, bears repeating.

Remember that this seminar is not intended to discuss any policy or any interpretation of the draft ENDS PMTA guidance, which is available for public comment. We're not going to be able to answer specifics regarding your product. We're not doing one-on-one consultations. So if you have any of those questions, your best bet is to send them to AskCTP@fda.hhs.gov or request a meeting. And I think in the first session we actually gave you pretty specific instructions and reference areas for where to request a meeting.

So as an example, one of the questions was what evidence or study endpoints would satisfy FDA's recommendation for an

assessment of abuse liability? And this could apply to any kind of product or any kind of study. We're not going to be able to answer those specific types of questions in this forum.

Also, if you're asking about study specifics regarding margins of error or what we would accept as endpoints, again, in this forum we're not going to be able to answer those questions for you, okay?

So the appropriate place for that would be to have a meeting, or again, if you have specifics regarding your situation, you could also send your questions to AskCTP@fda.hhs.gov. Okay. So I just wanted to make that point clear.

DR. DRESLER: Yeah. And one of the things for me, when I was talking about the Kentucky reference cigarettes, some people heard Kennedy. So I don't know I did say Kennedy, so who the heck knows what's a Kennedy cigarette. I don't know. I shouldn't say that, there might be some Kennedy cigarettes. I was referencing the reference cigarettes, which are Kentucky reference cigarettes, and those are the ones that are not intended for human use, okay? So Kentucky reference cigarettes.

Okay, on to our last session, and this session is entitled

Consumer Perception and Qualitative Studies of Investigational Tobacco Products. And our first presenter is Dr. Ben Apelberg, who will be speaking on Principles Related to the Likelihood of Tobacco Product Initiation and Cessation.

Dr. Apelberg.

DR. APELBERG: Thank you, Dr. Dresler.

My name is Ben Apelberg. I'm the Acting Division Director in the Division of Population Health Science at CTP's Office of Science, and today I'm going to be speaking about Principles Related to the Likelihood of Tobacco Product Initiation and Cessation.

Just a brief overview of what I plan to touch on today: I will start with laying out what's in the Federal Food, Drug, and Cosmetic Act with respect to the population health standard for premarket tobacco product applications. I'll then discuss a bit about the role of tobacco use behaviors on population health and then give you some examples of approaches that have been used for studying the potential for tobacco product uptake, or initiation, or tobacco product quitting, or cessation.

So when evaluating premarket tobacco product applications, the Federal Food, Drug, and Cosmetic Act requires, among other

things, FDA to evaluate the risks and benefits to the population as a whole. This includes the increased or decreased likelihood that existing users of tobacco products will stop using such products, and the increased or decreased likelihood that those who do not use tobacco products will start using such products.

So Part A in this quote refers to cessation or quitting the use of tobacco products, and Part B refers to initiation or uptake of tobacco products among those who might never have used or might have previously used tobacco but then subsequently quit. But when we start to try to understand the impact of a new tobacco product on the population as a whole, it's clear that there are a number of use behaviors that can influence population health embedded in the discussion about initiation and cessation.

So, for example, tobacco users may switch completely from the product they're currently using to the new product. Nonusers may initiate the new product, and this can include those who have never used tobacco previously or those who have used tobacco and have subsequently quit. Once an individual starts using this new tobacco product, they may progress -- they may be more likely to adopt other products that pose

higher levels of risk to the individual user.

And additionally, tobacco users may switch to the new product rather than quitting tobacco completely, or they may switch to the new product while continuing to use their current product, thus becoming dual users or poly-tobacco users.

And so these potential behaviors can influence population health. So, for example, if a new product poses less risk to individual users than other products on the market, there could be a benefit to individual users who switch completely, assuming it doesn't delay cessation, or they don't opt to switch instead of using an FDA-approved therapy for cessation. However, since no tobacco products are safe, you know, if nonusers start using this new product, then that would be a public health concern.

So within the Federal Food, Drug, and Cosmetic Act, FDA is charged with considering these impacts on population health. And so over the next few slides, we'll talk about some of the types of studies that have addressed the potential for uptake, use, and cessation of tobacco products. And I'll also touch briefly on the use of population modeling, which has been used to integrate multiple types of information about behavioral patterns on population health as a whole.

So as I just mentioned, in addition to the health risk profile of a new product, the impact of a new product on population health depends in part on who ends up using those products and how they use them.

There's a growing body of evidence in the scientific literature that has begun addressing some of these behavioral research questions with respect to ENDS products in particular, and some of the typical questions in the scientific literature include:

- How likely are nonusers of tobacco products, particularly youth and young adults, to initiate and use ENDS products?

- Does ENDS use increase the likelihood that never smokers will start smoking cigarettes?

- Does ENDS use increase the likelihood that existing cigarette smokers will stop smoking, and if so, what features of ENDS products may influence this likelihood? And then

- How likely are smokers to become dual users of cigarettes and ENDS, and is this dual use likely to be sustained or transient?

So when we talk about initiation or cessation, generally we're talking about a process by which individuals are changing

their use behavior. In the scientific literature, product uptake or initiation and quitting or cessation have been defined in a variety of ways.

Typically among youth, studies have focused on understanding the initial stage of trial or initiation, so in other words, going from never use of a product to ever having tried the product. In addition, past 30-day use is a measure of recent use that's typically used to assess youth tobacco use behavior as well as precursors to behavioral outcomes, such as perceptions or intentions to use.

Among adults, studies typically have focused on some level of established use frequency. So one of the traditional measures of use is current use every day or on some days.

Now, cessation is typically defined as currently not using a given product by individuals who reported prior, typically sustained use of the product. The specific definition used to define cessation, though, may vary depending on the purpose of the research question. So, for example, it may be based solely on self-reports or may include a measure of biological confirmation to ensure that no tobacco products were used.

Recently, it can be defined as a sustained abstinence over a period of time or abstinence at a given point in time. In

studies that follow individuals over time, cessation can be assessed at different points in time. And what's really important, though, is that clear definitions and rationale are provided to support meaningful interpretation of research findings.

So before we get into some of the specific types of studies that could be informative, I just wanted to reiterate that, as I mentioned earlier, FDA is required to evaluate the risks and benefits to the population as a whole, including to tobacco users and nonusers. However, as you've heard previously, it applies here as well. FDA does not currently require specific studies, particular studies to be conducted on the potential for tobacco product uptake or cessation.

What I will do in this presentation is offer some examples of the types of studies that have been used in the scientific literature, and it may inform an understanding of the potential impact to users and nonusers. This is not meant to imply that all of these studies are necessary or even that any specific study that I mentioned is necessary to support a product application. There may be other types of evidence related to impacts to nonusers and users that I don't mention here. So just an example.

Okay. So if we think about some of the different types of studies that may provide information on the likelihood that existing users will stop or nonusers will start using tobacco products, these include, but are not limited to, some of the following that I've listed here. You just heard, in the previous session, Dr. Schroeder talking about nicotine exposure or clinical pharmacology studies, and they can provide information on the rate and extent of nicotine delivery of ENDS products to users and therefore could inform an understanding of the product's ability to deliver sufficient nicotine for greater product acceptance or replacement.

A few speakers have talked about actual use studies. If such studies are available, they could also include assessments of the extent to which -- as individuals are using a new product, how their tobacco use behavior with respect to their existing product changes. Do they cut down on use of that product? Do they stop using it, or do they sustain use?

Market research studies may be available, both quantitative and qualitative research designed to identify and characterize the potential market and consumer preferences related to a particular product.

In the next presentation, Dr. Portnoy is going to talk

about consumer perception studies, so studies of factors that may predict future tobacco use uptake, such as studies of perceptions and behavioral intentions may be particularly useful and informative to understanding initiation and cessation. Of course, studies that directly assess behavior, whether they're observational or cross-sectional surveys such as the ones that Catherine Corey talked about yesterday, or longitudinal prospective studies that allow for assessing changes within individuals over time, like the PATH study, could provide useful information.

And finally, in the literature there are a number of randomized trials of product switching that have been conducted to look at the extent to which individuals, smokers in many cases that are provided with e-cigarettes, whether that increases the likelihood that they quit smoking completely.

So that gives you a sense of some of the different types of studies that are out there that might inform thinking about impacts to users and nonusers.

And I also wanted to note that there may be a variety of sources of this information as well. So we heard yesterday and throughout some of the talks today discussions of utilizing the published peer-reviewed literature, and Dr. Christensen noted

in her talk some of the general principles to keep in mind, specifically that a clear and transparent process be used to identify, evaluate, and report on that type of evidence.

Dr. Lindsey also talked about, in her presentation, that if relying on literature that's not for a specific product but for a different product or a category of product, it would be important to provide a clear scientific rationale and justification as to why that information can be extrapolated to the product of interest.

So there is a growing body of evidence in the literature. There may be analyses of existing data sources that could be conducted, such as the national surveys and PATH data that Catherine Corey talked about. Once again, I'm keeping in mind the limitations that she described in terms of the fact that most of that data is category or class specific, not brand specific, as well as original scientific investigations that you may choose to conduct on any of the studies we just talked about or other types of designs.

Population modeling may also provide insight into the impact of different patterns of initiation and cessation on population health. So in the scientific literature, these types of models have been used by researchers for a number of

purposes, including in the context of tobacco. This includes examining the potential impacts of new products or policies on tobacco use behaviors and some measure of population health. They can be useful for integrating information about both impacts to users and to nonusers, to assess the impacts to the population as a whole. They can be used to evaluate the different conditions that may result in benefits to health versus harms to health, as well as identifying areas where further investigation may be needed to refine particular inputs.

I did just want to note by way of example, one example of this kind of model is a project in a paper that I worked on that was published in *PLOS ONE*, and the reference is down below. The goal of this model in this paper was really to project the impact of cigarette smoking in the U.S. over time, in this case, on premature mortality, and then to examine the impact of a hypothetical new product with a lower risk than cigarettes, under different assumptions of product uptake and cessation, so that we could examine under what conditions we might expect to see benefits or potentially harms. And not surprisingly, the model results show that those impacts are particularly sensitive to the factors that we're talking about

today, so clearly the risk of the product, how harmful is the product and how harmful is it relative to other products on the market, as well as the extent to which product initiation, switching, or dual-use behaviors would occur.

In considering the impact of a new product on the population as a whole, there may be different vulnerable or susceptible populations to consider. One particularly vulnerable population that I did want to highlight is youth. I'm sure that a lot of people -- most people are aware that the majority of tobacco product initiation occurs among youth, and one of CTP's key public health goals is to prevent youth from starting to use tobacco products. So as a result, you know, this is a major area of focus in the research community, including in the context of ENDS use.

I did also want to remind people -- I think you've heard in a few other talks that we do have an example of an application or applications that did receive marketing authorization under this pathway, and the technical project lead memo, which is a very detailed summary of that decision, is available on CTP's website, and that might be informative to understand some of the types of information that were provided to provide some insight into the impacts on -- potential

impacts on users and nonusers. This included studies on consumer perception, clinical pharmacology, and nicotine exposure, as well as a body of evidence from the peer-reviewed literature related to product receptivity, cross-sectional observational studies, as well as longitudinal studies of behavior. So that's just there as a way of example.

So, in summary, I wanted to just highlight some of the key principles that I wanted to make sure you take away from this talk.

The Federal Food, Drug, and Cosmetic Act requires the FDA to evaluate risks and benefits to the population as a whole, including the likelihood that existing tobacco users stop and nonusers start using tobacco.

General principles would suggest that multiple lines of evidence would strengthen an argument related to likelihood of tobacco product initiation and cessation, and I provided some examples of the types of information that could be useful.

In the scientific literature, initiation and cessation have been defined in different ways. It's important that clear definitions and rationale are provided for how they're being defined in any particular setting in order to support meaningful interpretation of research findings.

Once again, best practices for reviewing a body of literature include clearly describing the methods used to identify and evaluate that evidence. And if utilizing data for similar products but not the product of interest in an application, it's clearly important to describe the scientific rationale and justification for such an extrapolation.

And then, finally, a reminder that youth are particularly susceptible to the initiation of tobacco products, and preventing youth tobacco use is one of CTP's key public health goals and an area of focus.

And with that I'll stop.

(Applause.)

DR. DRESLER: Thank you, Ben.

Our next presenter is Dr. David Portnoy, a social scientist within our Division of Population Health Science, and he will be speaking on Consumer Perception Studies.

DR. PORTNOY: Good morning. So as Carolyn mentioned, I'm David Portnoy. I am a team lead social scientist in the Office of Science at CTP, and today I'll be speaking on Consumer Perception Studies.

First, I'll provide a brief overview of what consumer perceptions are and give some general definitions. Next, I

will present some examples of the types of outcomes typically included in consumer perception studies of tobacco products. And finally, I'll discuss some general principles for the design, conduct, and reporting of these types of studies.

As we've seen many times both today and yesterday, this slide lays out the two key factors to be considered in a determination of if a product is appropriate for the protection of public health when considering the population as a whole. So my presentation today will focus on how consumer perception studies may be used to speak to these factors of the likelihood of initiation and cessation.

Previous talks have discussed some potential sources of data or information that could be used to make the argument that a specific product is appropriate for the protection of public health. These include existing data such as national surveys or in-market data on current users of a product as well as relying on the existing scientific literature.

In addition to existing sources of data, data on a specific product and specifically consumer perceptions of that product could be used to estimate the likelihood of initiation and cessation.

So today I'll focus mainly on consumer perception studies

conducted about a specific product. In the next talk, Dr. Margolis will give more information on qualitative methods which may be combined with consumer perception studies to help inform the development of these studies and provide additional information.

As noted at the bottom of the slide, combinations of various types and sources of data, along with appropriate justification and explanation of how these different sources of data fit together, may also be an approach taken.

So here we see text taken from Section 6 of the draft guidance on PMTA for ENDS, available for comment, that discusses some aspects of consumer perceptions. I've underlined a few phrases on this slide and the next that are the most relevant to my talk today.

As you see from the slide, the draft guidance notes different types of consumer perception outcomes, such as how consumers perceive the product risk and that examples of such data may come from various sources, including "data you collect."

In this section of the draft guidance, I have underlined additional information on different types of perceptions, including perceptions of product risk, both absolute and in

comparison to other categories of tobacco products, which I'll talk a little bit more about later, as well as the different groups that such studies may be conducted with, such as current ENDS users, nonusers, and other tobacco product users.

So first let's define what consumer perceptions are. Different scientific disciplines may have slightly different definitions and names or terms, but here I lay out some overarching definitions.

Perceptions are widely included in many theories of consumer psychology and health behavior as precursors to specific behaviors. Generally, they include in the scientific literature beliefs, attitudes, judgments, or perceptions. In the context of studies on tobacco products, these perceptions often focus on the appeal of the product and the perceived health risks of that product, both in absolute terms as well as relative to other products or to quitting all tobacco use. They may be relevant to whether consumers are interested and they eventually use a specific product.

These perceptions can also include sensory expectancies, that is, what sensory experience consumers believe they will have using the product, including factors such as taste, smell, and others.

In addition, there may be other types of perceptions that may be relevant to if consumers are interested in and eventually use a specific product not included in this list.

The next step in many theories of behavior are intentions. These are thought to be more directly related to behavior, and they are influenced by the perceptions noted earlier. For example, a product with low appeal may translate into low intentions to use it, whereas another product which is perceived to have low health risk and positive sensory expectancies may result in some consumers intending to try or use the product.

On this slide and the next one, I'll be presenting some examples. So here I'm presenting a non-exhaustive list of some outcomes that researchers generally consider to be part of consumer perceptions that may be relevant to studies of tobacco products.

First, I list appeal, including the novelty of the product, beliefs about positive attributes of the users of that product as well as beliefs about positive attributes of the product itself; the perceived health risk, and this is both overall, so in absolute terms or to overall health as well as linking to specific relevant disease outcomes, and all of these in the context of both absolute measures of perceived risk as well as

compared to other products or to quitting all tobacco use altogether. In addition, in this category, the perception of addiction risk is a type of perception often included in these kinds of studies. Finally, sensory expectancies or reports of the product taste, flavor, strength, or use experience, satisfaction, which there was a question about earlier, could also be a type of perception which may be associated with future uptake of specific products.

On this next slide I have some examples of the types of measures of intentions that researchers generally use in studies of tobacco products. As noted earlier, intentions may be in part informed and influenced by perceptions such as appeal, perception of the health risk, and other factors. Thus, intentions may serve as an intermediate factor between perceptions and behavior.

And so some examples of intentions include the likelihood to purchase among nonusers or users of other similar products, users of other types of tobacco products such as cigarettes; as well as intentions to try a specific product in the near future among different groups, including ENDS users and nonusers as well as users of other products; the intention to use a product either instead of or in addition to another currently used

tobacco product, similar to what Dr. Apelberg was talking about earlier; as well as the intention to stop all tobacco use. The final two examples include the willingness to try the product if offered by a friend, which is the type of measure often more commonly used with youth, as well as reported reasons for use among current users of that product.

Studies of consumer perceptions generally follow established methods such as the use of best practices for questionnaire design to avoid introducing bias and to ensure that any data collected is valid. One such example of a best practice is given in a link under the first bullet point, although there are many different examples of best practices which you should be able to quite easily find.

In addition, the size of the sample in these types of studies can vary depending on the research question, but usually a clear rationale for the sample size is given based on factors such as practical considerations, the statistical power to detect effects, and other relevant factors.

The use of validated items whenever possible allows for the data collected to be compared to other studies and also ensures that any data collected are measuring what they are intended to measure. Along those lines, clearly defined aims that are

specified before data collection begins allows for transparency. Overall, a clear explanation of the methods and sample included in the study allow others to better understand the results and context. As in all studies with human subjects, these studies consider protection of human subjects as a critical element.

Finally, reports of these studies, such as those that can be found in the scientific literature, usually include a full reporting of the study protocol, measures used, the recruitment strategy and sampling, the characteristics of the sample, the analysis, and any other relevant aspect of the study. This allows for a full and complete understanding of the study, the results, and the conclusions drawn based on those results.

So on the previous slide, one of the general principles was the well-explained and justified methods and sample, and on this slide are some examples of the types of information that is typically included in report summaries or scientific manuscripts detailing the sample and methods used.

These include a full description of the recruitment methods and sources, the demographics of the sample, including tobacco use status or other relevant factors, what information was obtained from each group or if all items were assessed in the entire sample, as well as information to assess the

representativeness to the larger population or the ability to generalize the findings. So, stated another way, do those in the study represent the larger group from which the sample was taken and to which conclusions are drawn? And in doing so, a discussion and explanation of the sampling and weighting procedures is important.

In consumer perception studies of tobacco products, there may be different groups of participants included in the study, depending on the specific study aims. Some groups that researchers typically include in such studies are never users, both never users of a specific product or never users of any tobacco product; current tobacco users, including those who are dual or poly-users with other tobacco products as well as those interested in quitting all tobacco use. Another group often included are former tobacco users, either of the product of interest or former users of other tobacco products. In addition to selecting the study sample based on tobacco use status or demographics, the inclusion of populations that may be vulnerable to tobacco use or those for whom tobacco use presents unique issues may be considered. There's no one definition of vulnerable populations. So who is considered a vulnerable population may vary depending on the situation, product, or

other factors. But as we heard in a previous talk, youth are one population which are often considered to be a vulnerable population because of their well-documented use of tobacco products and the effects of exposure to nicotine, the potential for long-term addiction and future long-term use and negative health effects from that use.

So although there is no statutory requirement from FDA that requires that data be collected directly from youth, youth are considered part of the population as a whole, which is the basis for FDA to determine if a product is appropriate for the protection of public health.

Often in the scientific literature, researchers will extrapolate data from young adults to youth, use existing scientific literature, or use a combination of approaches and data sources to draw conclusions about perceptions or intentions of tobacco products among youth.

So, in summary, consumer perceptions are widely accepted in the scientific literature as precursors to use behavior, and they may directly inform the likelihood of initiation or cessation among certain groups.

Consumer perceptions may be useful data, even if real-world or in-market data already exists. And these sorts of data can

be used in multiple ways, either to provide additional context to other kinds of data; such as observational behavioral studies; they may be used as a justification for the bridging of data between existing scientific literature and other studies; or they may be used as standalone evidence to estimate potential behavioral effects.

So I'll conclude there. And I thank you.

(Applause.)

DR. DRESLER: Okay, our next presenter is Dr. Katherine Margolis, who will be speaking on Qualitative Studies, and she is a social scientist within our Division of Population Health Science.

DR. MARGOLIS: Great. Thank you so much. As Carolyn just mentioned, I'm Katherine Margolis. I am a social scientist in the Office of Science at the Center for Tobacco Products, and today I will be talking about Qualitative Studies.

The overall agenda for what I will be talking about includes the following: I will be talking about showing that the new tobacco product is appropriate for the protection of public health, I'll be giving an overview of qualitative research, and I'll be talking about examples of types of qualitative research.

So now we are going to talk about showing that the new product is appropriate for the protection of public health. This slide includes information from Section 910(c)(4) of the Federal Food, Drug, and Cosmetic Act and provides the basis of how a product can be determined appropriate for the protection of the public health. I know this slide has been shown in several other previous sessions, so I will not read it for you verbatim, but it does form the basis for the studies that we will be talking about.

So now I'm going to delve into the overview of qualitative research. So qualitative research is generally considered a descriptive research method that uses in-depth studies of people and produces findings not arrived at by statistical procedures. It is only one methodology, and other sources of data have been discussed in previous talks, including the consumer perceptions studies that Dr. Portnoy just discussed, the literature review session that we heard yesterday, and the national estimates of e-cigarette use session that we heard yesterday as well.

Qualitative research methods are generally concerned with beliefs, perceptions, and experiences that cannot be expressed numerically. They describe social phenomena as they occur

naturally. There are no variable manipulations as you might have in other types of research. And they often take an inductive approach and are used to develop concepts and theories. An inductive approach typically starts with observations that may be used to formulate tentative hypotheses that can be explored later. Inductive reasoning is more open ended and exploratory than deductive reasoning.

Generally, qualitative research consists of collecting data, interpreting and organizing the data, and then reporting the findings. So it's a three-step process.

Now we are going to discuss examples of types of qualitative research. One type of qualitative research is an in-depth interview. In-depth interviews consist of conducting intensive individual interviews with a small number of respondents to explore their perspectives. In-depth interviews are useful when you want detailed information about a person's thoughts and behaviors or are exploring new issues in depth. Interviews can vary in the level of structure. An example of using an in-depth interview would be conducting in-depth interviews with current users of cigarettes to explore how perceptions of e-cigarettes are associated with use intentions. These findings may then be used to create a survey instrument.

A survey instrument is a standardized questionnaire administered to a sample of respondents. This is often a part of quantitative research.

Cognitive testing is also a type of qualitative research. It is a method used to assess questionnaire items. Specifically, it can be used to collect additional information about responses, evaluate the quality of a question, and understand whether the question gathers the intended information. It typically either uses a "think aloud" technique or verbal probing. An example of cognitive testing is testing a survey instrument to understand how respondents interpret the questions and instructions.

Focus groups are another type of qualitative methodology. A focus group is a small group focused discussion guided by a trained facilitator. The group's composition and discussion are carefully planned to create a nonthreatening environment in which people are free to talk openly. There are typically about 8 to 10 participants, and they can yield a lot of information. They can be used to explore how people interact with and influence each other.

An example focus group would be with adult users of another tobacco product exploring factors associated with

switching to the new product or using both products, also known as dual use. These findings will then be used to develop more generalizable research.

There are several advantages and disadvantages to qualitative research that must be considered. Qualitative research provides more detailed information than what is available through other data collection methods such as surveys, as it is a deeper dive into an individual's thoughts, feelings, and behaviors.

It provides in-depth understanding of participant motivations and feelings, as you can ask participants additional probing questions to understand and clarify their thoughts, beliefs, and perceptions. It also allows participants to have more control over the content of the data collected. Participants are able to use their own words or their own language and terminology. Therefore, qualitative research looks deeper and provides more information than simply analyzing ranks or counting the number of responses as is done in quantitative research.

The methodology for qualitative research is more flexible, as it is generally open ended. Other less flexible methodologies, such as surveys, require the standardization of

data collection to allow statistical comparison.

There are also a few disadvantages to qualitative research that must be considered. First, qualitative research is prone to bias. Bias is any tendency which prevents unprejudiced consideration of a question. Qualitative research results in data which is not objectively verifiable. Interviewers and facilitators must also be appropriately trained in qualitative research techniques. If they are not, this can also be a source of bias.

Qualitative research is also time and resource intensive. It is not possible to automate qualitative data collection as effectively as you can automate quantitative data collection. Therefore, it is often time consuming and expensive to gather large amounts of data, as would be typical for quantitative research studies.

As mentioned before, qualitative research is also not generalizable. Generalizability is the extension of research findings from a study conducted on a sample population to the population at large.

A few methodological principles to consider when using qualitative data: Some of these include having clearly defined and pre-specified aims, using established methods, obtaining

human subjects protection, having a full description of recruitment, data collection, methods, your strategy for analysis, your transcripts and the summary of results, as well as discussion of study limitations.

Now I'm going to put up a few different types of resources for qualitative research methods. There are many different types of resources that can be consulted, but here are a sampling of websites and books that address qualitative research.

Great. Thank you very much.

(Applause.)

DR. DRESLER: Okay, our final presentation before the panel and questions will be given by Dr. Priscilla Callahan-Lyon, and she will be speaking on Investigational Tobacco Products and Support for Premarket Tobacco Applications.

Priscilla.

DR. CALLAHAN-LYON: So good morning again. I introduced myself earlier, but this time I'm going to be discussing investigational tobacco products and how studies involving investigational tobacco products might be used to support a premarket tobacco application.

So during this talk I will give some definitions, I will discuss interacting with FDA with regards to investigational tobacco products and requesting to use an investigational tobacco product, and how an ITP study result may be used to support a premarket tobacco application.

An investigational tobacco product: In the September 2015, draft guidance on use of investigational tobacco products, which is available for comment, it describes an ITP as a new or modified risk tobacco product that is not legally marketed, or a tobacco product that is required to comply with a tobacco product standard and that does not conform in all respects to the applicable tobacco product standard and is intended for investigational use.

So this means that a new tobacco product or a tobacco product on the market under the compliance policy outlined in the deeming rule, which is then used in a study, is considered an investigational tobacco product.

So what is a new tobacco product? A new tobacco product is a product within the meaning of Section 910(a)(1) of the Federal Food, Drug, and Cosmetic Act, or FD&C Act, if it was not commercially marketed in the United States as of February 15th, 2007, or if it was commercially marketed on that date but

has been modified and been commercially marketed after that date. So if it was on the market at February 15th, 2007, and it's been modified and subsequently marketed, it is a new tobacco product.

That leads to what is modification? Modification under 910(a)(1)(B) includes any change in the design, component, any part, any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine or any other additive or ingredient of a tobacco product. When a marketed tobacco product is modified, the modified product becomes a new tobacco product.

So now I'm going to discuss interacting with FDA, particularly with regard to investigational tobacco products. According to the September 2015 draft guidance on the use of investigational tobacco products, which is available for comment, any new tobacco product that is on the market under an exercise of FDA's enforcement discretion is an investigational tobacco product if it is intended for investigational use.

So a new tobacco product, which was defined a couple slides ago, and that means one that was either marketed after February 15th, 2007, or if it was changed and then marketed after February 15th, 2007, is considered an investigational

product if it is intended for investigational use. So if the intent is to use one or more of these products in a study, it becomes an investigational tobacco product, and it doesn't matter whether you're the product manufacturer or not.

However, Section 910(g) of the FD&C Act gives FDA the authority to issue regulations to exempt tobacco products intended for investigational use from the requirements of Chapter IX of the FD&C Act, including premarket submission requirements. These regulations have not yet been issued. So for now, the Center for Tobacco Products recommends discussing the use of an investigational tobacco product with us prior to conducting the study.

So finalization of the deeming rule did create a little bit of an issue for sponsors. As noted earlier, the newly deemed products that remain available on the market due to an enforcement discretion, such as e-cigarettes, are not legally marketed, and therefore they are investigational tobacco products if they are used for an investigational purpose. Therefore, if these products are used in a study, they are an investigational tobacco product.

Furthermore, the draft guidance for the use of investigational tobacco products, available for comment, states

that investigators should have adequate procedures in place to ensure that the investigational tobacco product is not commercialized.

So to deal with this issue, on October 12th of this year, FDA published a new guidance, "Investigational Use of Deemed, Finished Tobacco Products That Were on the United States Market on August 8, 2016, During the Deeming Compliance Periods."

This new guidance clarifies that FDA does not intend to enforce the premarket authorization requirements for the newly deemed, finished tobacco products that were on the United States market on August the 8th, 2016. FDA is clarifying that the compliance policy described in the preamble to the deeming final rule applies to such products even if they are used in a scientific investigation.

So to clarify, if the product was on the market August 8th, 2016, and it is to be used in an investigation without being modified, FDA does not intend to enforce the premarket requirements, and the study may be conducted while the product remains commercially available under the deeming rule compliance policy. If the product is modified, it becomes a new product, and then we recommend that the study be discussed with FDA.

So requesting to use an investigational tobacco product: To request the use of an investigational tobacco product, we ask that you submit a request to CTP. CTP assesses the administrative properties of the submission. That ensures that the study involves an investigational tobacco product that is under CTP jurisdiction and that the submission can be assessed, that is, it's written in English, it can be opened, the products are identified, and there is a protocol included.

CTP will then conduct a multidisciplinary scientific assessment of the use of the investigational tobacco product in the context of the proposed protocol, and then the sponsor is notified of our assessment.

As described in the September 2015 draft guidance, available for comment, the primary focus of the CTP assessment is whether use of the product or products, as proposed to be studied, raises concerns for human subject protection. CTP also assesses the proposals for studies using investigational tobacco products to determine if the sponsors can ensure that the studies are well controlled and that the data derived from the studies will be reliable.

So now I'm going to discuss how these study results might be used to support a PMTA. As discussed in the draft guidance

on PMTA for ENDS and in the September 15th draft guidance for use of investigational tobacco products, both of which are available for comment, studies may provide data to support a PMTA. The data derived from nonclinical or clinical studies may support and fulfill some of the nonclinical and clinical PMTA requirements.

The other point I think is very important is that information related to any sort of adverse effects involving similar tobacco products may significantly contribute to the FDA assessment of your tobacco product and whether the product is appropriate for the protection of public health.

To facilitate any reporting of these adverse effects or experiences, FDA CTP encourages the use of the safety reporting portal, and I've provided the link here. The portal can be used by anyone, but there are specific pathways in the portal for investigators, manufacturers, and healthcare providers, as well as a more general portal for consumers.

Group accounts can be established so that all reports related to a single investigation or a single group can be associated with the same account, which makes completion of some of the forms easier.

We are developing webinar training modules, but the portal

can be used now. And training, which will provide a few additional tips, is not necessary in order to be able to complete a report.

If you are considering conducting a nonclinical or clinical study and have questions related to investigational tobacco products, I've included the contact. And I also have included links to the guidances, the draft guidances, as well as the safety reporting portal which has been referenced in this talk.

Thank you.

(Applause.)

DR. DRESLER: Good. Questions are coming in. I had one that came in previously prior to the meeting, so let me start with it. Will qualitative data alone provide sufficient data in a PMTA review?

Dr. Margolis.

DR. MARGOLIS: Qualitative data likely will not be -- will not provide a raw picture of things. It would depend on the study's purpose and the information that you're trying to collect with the qualitative data. Usually qualitative data is used in conjunction with other research methodologies, but again, it would depend on what you're trying to assess with the

data.

DR. DRESLER: Okay. Is it possible to get a list of all of the public studies cited by the existing PMTA marketing authorizations for tobacco products?

So, again, this goes to the PMTA that we've mentioned a few times, so you could look and ask for a Freedom of Information request for the applications. And I'm not sure if that answers the person's questions, but if you want the current PMTA that's been reviewed, you could do a FOIA request to get that list of the public studies that were cited. And if that doesn't answer your question, please ask again. So I'm not sure if that's the exact interpretation that you wanted.

More questions: So this is investigational tobacco products, Dr. Callahan. Investigational tobacco products are only products that are not currently on the market, correct? If my product is on the market and I wish to engage in studies in support of my PMTA -- August 8th, 2018 [sic] -- do I need to submit an ITP request?

DR. CALLAHAN-LYON: So if your product was on the market on August the 8th, 2016 and you wish to use it in a study, then you can use it in the study unmodified, as long as it was on the market prior to that date. I think that's the question

you're asking.

DR. DRESLER: I think that's getting to it. So it's basically it was on the market and it's unmodified.

DR. CALLAHAN-LYON: Right. If it was on the market August 8th, 2016 and you are going to use it in a study unmodified, you may do that.

DR. DRESLER: Without going to CTP --

DR. CALLAHAN-LYON: Without coming to CTP. That's what the new guidance is stating.

DR. DRESLER: Okay. So if you modified it --

DR. CALLAHAN-LYON: If it is modified --

DR. DRESLER: -- in September of 2016.

DR. CALLAHAN-LYON: -- then it is an investigational tobacco product, and we ask that you come and speak with us before using it in a study.

DR. DRESLER: If qualitative research is not generalizable, how can it be useful in evaluating population risk to benefits of a new ENDS product?

DR. MARGOLIS: Sure. So some of the examples that I gave in my presentation show different ways qualitative research could be useful. So you may use it to cognitively test survey items to find out how different user groups perceive the items

and interpret the items or the instructions in a survey. It can be used to pilot test different things. You may use interviews or focus groups to find out the terminology that different users or participants may use, and that may help you inform or learn how to write about survey items later on for different forms of quantitative research.

So I think that most often, in the general research sense, people use qualitative research to inform quantitative research. So you may use it as a pilot test. You may use it to understand thoughts or feelings and deeper ways. So it's often used in conjunction with other types of research. But again, it would depend on what you're trying to assess with it to see if it's the best format or type of research to use. All different types of research have different advantages and disadvantages, so you really need to look at the question that you're asking to find out if that is the best research methodology for you to use.

DR. DRESLER: Okay. A question on the safety reporting portal. Are companies able to access consumer reports from the safety reporting portal for their particular ENDS product?

DR. CALLAHAN-LYON: I don't think you can see a report other than the ones that you submit. But if you want to send a

question in to AskCTP, we can confirm that for you.

DR. DRESLER: Okay. Dr. Portnoy -- well, I'll let anybody, but I think this is for you. Re youth appeal, how can sensory appeal be assessed? So for youth, how can sensory appeal be assessed?

DR. PORTNOY: Sure. So this gets at the difficulty in trying to provide information about appeal of products among youth, without directly doing studies with them obviously. There are a number of ways to get data either about youth or from youth, and one way, as I mentioned in the talk, is to extrapolate from young adults and their use, their beliefs. There may also be ways to look at other sources of data about youth sensory expectancies or their preference, for example, for different flavors both in tobacco as well as for other consumer products.

And so there may be ways to bridge data from, for example, other consumer products as well as relying on existing scientific literature to try to get that sort of information on those sensory expectancies among youth or young adults.

DR. DRESLER: Okay. Dr. Margolis, so qualitative analysis and the inclusion of expert -- subject matter experts' interviews is standard practice among market and behavioral

predictions. So methodological leaders such as Clotaire Rapaille -- and I hope I said that correctly, because my French isn't so good -- have established extensive protocols commonly used among market analysts for their predictive values. So can you speak to the FDA's view on these types of weighted qualitative behavioral analyses? So I think it's asking the question of did you mention or is a good study a weighted qualitative behavioral analysis?

DR. MARGOLIS: I'm not exactly sure what the question is asking. Usually weighted implies a statistical weight, which would make it more of a quantitative study. So I think that we would -- I would need to have more detail about the study design to understand what's truly being asked. But in an application, you can always provide a rationale and justification for why that data methodology would be appropriate or how it's used in other contexts and how it can be used in this application.

Dr. Portnoy, did you want to jump in?

DR. PORTNOY: Yes. So to clarify, the types of qualitative research that Dr. Margolis was talking about was really qualitative research with consumers, so users and nonusers. I think what this question is asking about is more

expert elicitation methods that are looking, for example, at market trends, and that's a slightly different kind of information.

As you've been hearing throughout the past day and a half, there are many ways to pull data and information from various sources. And so if using more of an expert elicitation protocol or market trends analysis or something like that, if you feel like that may be something to add to a package along with all of this other information, that could be one potential source of information to include. But I think that's a little bit separate from sort of a qualitative in-depth interview, focus groups, cognitive testing that Dr. Margolis was talking about, which again is really more focused on potential consumers of these products.

DR. DRESLER: And I think, Priscilla, this would be for you. Can you speak to whether providing ENDS to clinical study subjects implicates the regulation's ban on free samples? So when you're doing a clinical study and you're providing the products to the subjects, is that a free sample?

DR. CALLAHAN-LYON: That is not considered a free sample. If you have a subject that has been consented and signed all the appropriate forms and had the subject -- the study has

undergone adequate review and assessment for human subjects' protection, then that is not considered to be a free sample.

DR. DRESLER: So let me see if there are more questions. This is your last opportunity. Any questions coming in online? Thank you. Was there a reason why likelihood of use was used for meaning or measuring or addressing purchasing, but intention was used for measuring trial use and dual use? So was there a reason why likelihood of use was used for measuring or addressing purchasing, but intention was used for measuring trial use and dual use?

DR. PORTNOY: So I think that might have been from my presentation potentially. So in that slide that now you've seen many, many, many times, the standard for the appropriate -- appropriate for the protection of public health for the population as a whole includes the likelihood of initiation and the likelihood of cessation.

So part of the reason you've heard the word "likelihood" is because that comes directly from the statute as it relates to the PMTA process. When you're talking about consumer perceptions and specifically when I was talking about intentions, intentions are a measure which could inform that likelihood of use.

So those two things are not necessarily synonymous, but at the same time, if you're interested in using a measure of intention to inform the likelihood of initiation or likelihood of cessation through the likelihood of purchase, it would be helpful to provide a justification for why you believe such measures inform that standard for the likelihood of initiation or cessation.

DR. DRESLER: I'm seeing one more potential question, so hold on a moment. Anyone else? If you'll get those turned in. We still will be finishing very early, so I'm not holding you up from lunch very much. That, you're going to address? Okay.

(Pause.)

DR. DRESLER: So are there more questions for me to ask? We're going to have some closing comments by Dr. Chen, and she will be addressing some of the questions herself. But any others?

(No response.)

DR. DRESLER: Okay. So I don't see any others coming up for us or the panel. So thank you very much, panel. Excellent presentations.

(Applause.)

DR. DRESLER: And Dr. Chen.

DR. CHEN: Hi, I'm Ii-Lun Chen. I'm the Director for the Division of Individual Health Science. And in wrapping up, I just wanted to answer a few questions that have been asked.

If an ENDS product that was not on the market on August 8th, 2016 is planned for use in a study related to its potential use as a smoking cessation product regulated by CDER, is a CTP assessment as an ITP necessary? No. If you're using a tobacco product and studying it as a potential for smoking cessation, you need to follow CDER regulations, okay?

There was a question regarding when will the PMTA draft guidance be closed for comment? You can always continue to send comments in to guidances. So if you do have a comment you'd like to make on the ENDS PMTA draft guidance, please do so. We will review that.

And then there were two questions that were worded very differently, but I think they warrant a similar answer, so I'm going to read you the questions.

The routine answer for whether something should be included in the PMTA is nothing is required in the PMTA. If nothing is required in the PMTA, on what merits will the FDA deny PMTAs?

And then another question was what is critical

information, whether testing or research, that the FDA will focus on to determine if the ENDS products are safe for health? And I think what this gets to is that there's a difference in terms of required information and required studies, and I wanted to make that clarification.

So the Food, Drug, and Cosmetic Act, under Section 910, talks about required information FDA needs to receive in your submission to make an authorization decision, right, a Marketing Order or No Marketing Order decision.

And under 910(b)(1) it talks about needing full reports reasonably known on health risks. So we need to understand the likely health impact of your product. It talks about full statement of components, ingredients, additives, properties, principles of operation. So what is your product, right? What is your product? How does it work? How is somebody supposed to use it?

It also talks about needing to provide full description of methods, manufacturing, facilities, controls, packaging, and installation. So how do you make it? What's the process by which you manufacture this product and put it together?

It also talks about needing to reference a product standard. In the case of ENDS, we talked yesterday about that

there is no current reference standard, but you should probably just state that in your submission.

It also talks about needing to submit labeling and that the labeling should not be false or misleading, right? In another section, Section (c)(2) and (c)(4) also talk about information that FDA needs to assess, looking at the likelihood of initiation and likelihood of cessation. And separately we've talked about how you need to provide an environmental assessment to understand the product's impact.

So I think we've talked about multiple lines of evidence and the totality of evidence as being really important for us in order to determine, based on all the information you provide, whether that product is appropriate for the protection of public health.

Now, I know that we provided a lot of information, and it seems like an overwhelming amount of information, but what we tried to do today was to provide you general information on administrative process, as well as really provide general scientific principles that are important in doing scientific studies as well as really tools for you to use. How you use the tools and what tool to use is completely up to you. There's no predetermined package that FDA has envisioned as to

what a successful PMTA looks like. Really, you just need to answer the statutory requirements and give us enough information so that we know what is your product, how is it made, what is the impact, so if we were to say that product can go to the market, what's going to happen on a population level? What's the impact on users, nonusers? What is the behavior going to be in terms of transition? So that's kind of the information we're looking for.

And again, in terms of required studies, there are no specific required studies. But whatever you think you need to do to provide that information, whether it's publicly available literature or nonclinical studies, clinical studies, that's completely up to you. We did emphasize, though, that in terms of long-term health outcome studies like those multi-year health outcome studies or long-term carcinogenicity studies, those are not required or expected either.

So if you have further information that you would like to share with FDA in terms of how you're developing your submission and would like comment on that, you can submit a meeting request. If you have specific questions that are kind of smaller in scope, then you can submit them to AskCTP@fda.hhs.gov, or you can e-mail the Small Business

Assistance Program.

All right. So thank you very much for your time. We hope that we answered many of your questions, and if you continue to have questions, you have some resources available to you. So thank you very much.

(Applause.)

(Whereupon, at 11:43 a.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

THE PREMARKET TOBACCO PRODUCT APPLICATION FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS):

A PUBLIC SEMINAR

October 18, 2016

Hyattsville, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Tobacco Products.

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ED SCHWEITZER

Official Reporter

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2515 Saint George Way
Brookeville, MD 20833
301-924-1556