UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR TOBACCO PRODUCTS

+ + +

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

+ + +

October 17, 2016
8:30 a.m.

The Marriott Inn and Conference Center
University of Maryland University College
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

DAVID L. ASHLEY, Ph.D.
RADM (retired), U.S. Public Health Service
Director, Office of Science
Center for Tobacco Products

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

KIMBERLY BENSON, Ph.D.
Director, Division of Nonclinical Science
Center for Tobacco Products

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

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

SESSION 1: GENERAL INFORMATION

COLLEEN LEE, J.D.
Regulatory Counsel
Center for Tobacco Products

CALIOPE SARAGO, M.H.S.A.
Team Lead, Division of Regulatory Project Management
Office of Science
Center for Tobacco Products

JEFF K. SMITH, M.P.H.
Regulatory Health Information Specialist
Division of Regulatory Science Informatics
Office of Science
Center for Tobacco Products

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

SESSION 2: PRODUCT SCIENCE OVERVIEW

TIANRONG CHENG, Ph.D.
Chemist, Division of Product Science
Office of Science
Center for Tobacco Products

KOMAL SINGH, M.S.
Engineer, Division of Product Science
Office of Science
Center for Tobacco Products

STEVEN YEE, Ph.D.
Toxicologist, Division of Nonclinical Science
Office of Science
Center for Tobacco Products

GREGORY GAGLIANO, M.S.
Toxicologist, Division of Nonclinical Science
Office of Science
Center for Tobacco Products

SESSION 3: DATA SOURCES

CATHERINE G. COREY, M.S.P.H.
Epidemiologist, Division of Population Health Science
Office of Science
Center for Tobacco Products

CAROL H. CHRISTENSEN, Ph.D., M.P.H.
Epidemiologist, Division of Population Health Science
Office of Science
Center for Tobacco Products

SESSION 4: HEALTH RISKS

CINDY M. CHANG, Ph.D., M.P.H.
Epidemiologist, Division of Population Health Science
Office of Science
Center for Tobacco Products

JEANNIE LIMPERT, M.D.
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

INDEX

INDEX

M E E T I N G

(8:30 a.m.)

DR. DRESLER: Good morning, my name is Carolyn Dresler, and I'm with the Office of Science. I'm the Associate Director for Medical and Health Sciences, and I will be your moderator for these next 2 days.

So welcome to our information seminar on premarket tobacco applications, and we have a full day and a half or so, so we will have a series of presentations and then an opportunity for questions and answers, but we're going to start off with some opening remarks by our Office Director, Dr. David Ashley, the Director of the Office of Science at the Center for Tobacco Products.

David.

DR. ASHLEY: First off, let me just welcome everybody who is here in person and also the folks that are on the webcast. I'm glad to see you here, thanks for coming. I'm really glad you're here. For those of you who have seen me before in uniform, I am not in uniform anymore. I actually retired from the Commission Corps 5 months ago and switched over to being a civilian, so the uniform is put away. Just in case anybody was wondering.

FDA is committed to using the authority that's been granted to us by Congress to promote public health by reducing disease and death that results from tobacco use. In August 2016, the deeming rule went into effect; the deeming has extended FDA's regulatory authority to tobacco products which were not previously regulated. It also brought many tobacco product manufacturers under regulation who were not regulated previously.

We expect that because of the nature of the products that were deemed, more then will seek marketing authorization through the premarket review process. FDA is committed to a consistent, transparent, and predictable process for review of tobacco product applications.

So we try to communicate through as many means as possible. We've issued several regulations and guidances along with the deeming rule; we've developed webinars to inform manufacturers, and those are up on our website; we have updated our website, also, to make it easier for visitors to that site to find the information they need. We set up a call center to answer questions, and many of you have been sending in lots of questions, and we've been trying to respond to those as quickly and accurately as possible. We expanded the small business

assistance team to help inform small businesses how to conform with the law, and we continue to look for additional means to communicate to regulated industry. This informational seminar is one of those additional means.

The seminar is intended to try to improve understanding of the general scientific principles for evaluating ENDS, along with some administrative information to assist persons considering submitting applications for ENDS products under the premarket review pathway. Through the seminar, we especially want to provide information to manufacturers whose products are newly regulated and those who are not as familiar with how to approach an application.

We will be providing a lot of information over the next day and a half, but first let me be very clear, we are not saying that all the studies that we're discussing will be needed for a successful application. That is not the message that we want you to take away. In developing their applications, manufacturers can choose what information they believe would address the statutory requirements. We're trying to provide you as much information as we can so that you can make decisions about how to approach your applications. And there are many ways that applicants may be able to address

statutory requirements for FDA to make that finding that products are appropriate for the protection of public health.

In this seminar, we are not saying how manufacturers must address those requirements; that would only be done under notice and comment rulemaking. This seminar is intended to help manufacturers better understand the scientific principles for evaluating ENDS.

This is not the last effort we will make to communicate with regulated industry on these issues, but we hope it's beneficial and will answer some of the questions that have resulted from deeming of products under FDA regulatory authority.

Again, thank you all for attending. I'm glad to see so many folks here, and I understand there are a lot of people also that are on the web. And the person who is going to follow me is Dr. Kimberly Lindsey. Dr. Lindsey is a medical officer in the Office of Science at CTP, and she has been leading this effort in pulling together this seminar.

Kimberly.

DR. LINDSEY: Thank you, Dr. Ashley.

Good morning. I, too, would like to welcome you to the first day of the informational seminar on PMTA for electronic

nicotine delivery systems, which I will shorten to ENDS, products. I'm going to spend a few minutes providing you with an overview of this informational session and provide you with some logistical information.

The purpose of this informational seminar is to improve understanding of general scientific principles of evaluating ENDS products under Section 910 of the Federal Food, Drug, and Cosmetic Act, otherwise known as the FDCA.

We would like to address a few topics during this informational seminar.

Number 1, what information the FD&C Act requires to have an applicant to include in a new tobacco product application.

Number 2, some basic administrative processes involving the submission of a new tobacco product application.

And Number 3, breaking down some scientific terminology and discussion of established scientific principles for non-scientists, particularly in relation to developing an understanding of ENDS products.

The seminar will also aim to explain some scientific terms that are used in the draft ENDS PMTA guidance to further enable the public to provide comment. I do want to emphasize, however, that this seminar is not intended to discuss any

policy or interpretation of the draft ENDS PMTA guidance, which is available for public comment.

Section 910 of the FDCA requires that FDA deny any premarket tobacco product applications where it finds that there is a lack of showing that permitting such tobacco product to be marketed would be appropriate for the protection of public health.

Applicants are expected to provide, in a PMTA, information to support a showing that the new product is appropriate for the protection of public health with respect to the risks and the benefits of the population as a whole, including users and nonusers of the tobacco product. These studies must take into account or address the likelihood of initiation or cessation of the product, that is, the increased or decreased likelihood that existing users of the tobacco products will stop using the products and the increased or decreased likelihood that those who do not use the product will start using such products.

During the seminar, presenters will describe general established scientific principles that may be considered to develop an understanding of ENDS products related to the following: health risks of the product on users, nonusers, and potential exposures; the likelihood of initiation and cessation

by both users and nonusers of tobacco products; product use patterns; human factors; and abuse liability.

We acknowledge that ENDS present complex regulatory and scientific challenges and that there are strong opinions about these products and their potential impact on the public health. However, we do request that all seminar attendees be considerate and respectful of all speakers and other attendees and the information that is being presented.

There will be seven sessions during this one and a half day seminar; each session will be followed by approximately 15 to 20 minutes for questions and discussion. The seminar is being recorded, and the transcript and webcast recordings will be posted on our website when they become available in the near future.

For those of you who are attending in person, we have copies of a useful links document which contains many, but not all, of the hyperlinks that you will see in the presentations during the seminar. Those are available for you to pick up in the back of the room along with an agenda.

For those of you who are online, we will try to get this same information posted online with activated hyperlinks to the resources. You will be able to go back to this recording to

either find the links that are presented or to find the appropriate contact information. So do not worry about trying to quickly write down all the resource information as we go through the presentations because this will be available to you at a later time.

For those of you who have questions for a speaker or for a panel member and you are here on-site, please write your questions on one of the cards provided, using legible handwriting, and give the card to one of our volunteers. We are not addressing questions about policy or questions about your specific product or situation. If you have such questions, you are welcome to send them to AskCTP@fda.hhs.gov. If you are participating by webcast, you can e-mail your questions to the workshop e-mail address, which is workshop.CTPOS@fda.hhs.gov.

We will have a short break in the morning and then again in the afternoon today as well as the 45- to 50-minute lunch break. So we will ask that you please take all of your personal items and belongings with you when you leave the room. We will end the day at around 4:00 or 4:30 p.m.

Just a few more logistical details before we begin with the presentations.

For those of you who did not bring your own lunch, there are a few places to eat here on the campus, and there is a restaurant located in the lobby area. For those of you who brought your own lunch, there are a few areas around the immediate vicinity for you to sit and eat. During breaks, you can find food and beverages available for purchase at the kiosk area on the main level upstairs.

And then finally, restrooms can be found outside this room if you go to the left, all the way down the hallway to the right, and then you'll see the bathrooms on the right-hand side immediately across from the elevators.

Thank you. And so with that, I would like to turn the podium over to our moderator, Dr. Carolyn Dresler.

(Applause.)

DR. DRESLER: Okay, thank you.

Okay, we'll start out with the first session, which is one on general information, and we'll start out with Colleen Lee speaking on Good Guidance Practices at the FDA.

MS. LEE: Thank you, Carolyn.

Hi. I wanted to take a few minutes to talk to you all about FDA's good guidance practices and how they'll relate to the draft guidance on premarket tobacco applications for

electronic nicotine delivery systems, which we're calling ENDS PMTA draft guidance.

So I will first explain what good guidance practices are, then I'll explain what a guidance document is and if it binds any person to any specific actions. Then we will go over FDA's process for creating a guidance, and finally, I'll discuss what this all means in relation to the ENDS PMTA draft guidance and other guidances that you might hear at the seminar.

So what are good guidance practices? good guidance practices are FDA's policies and procedures for developing, issuing, and implementing guidance. They are regulations, so they do have the force of law. Good guidance practices allow the public to provide input on FDA policy; they prevent confusion as to what is required; they make clear what is the Agency's official policy and current thinking; they make clear what is binding, what is guidance, and what is neither; they make sure that policies and current thinking are communicated broadly and not just to a limited audience.

What is a guidance document? Guidance documents are prepared for FDA staff, applicants or sponsors, and the public, and they describe the Agency's interpretation of or policy on a regulatory issue.

What do we mean when we say a policy on a regulatory issue? This could include, but are not limited to, regulated product design, production, labeling, promotion, manufacturing, and testing. It could also be the processing, content, and evaluation of submissions, which we're talking about today, and inspection and enforcement policies.

Good guidance practices also tell us that the Agency may not use any other documents to communicate new or different regulatory expectations to a broad public audience for the first time.

Guidance documents are non-binding on any party, such as applicants, FDA, or the public, meaning they do not instill any requirements. For the public, this means the applicants may choose to use an alternative approach other than what is discussed in a guidance. However, if an applicant chooses to use an alternative approach, they must ensure that their approach still complies with any relevant statutes and regulations.

For FDA, good guidance practices mean that even though guidance documents are not binding, they do represent the Agency's current thinking. Therefore, FDA can only depart from a guidance's approach with appropriate justification and

supervisory concurrence.

So now that you understand a little bit about the purpose that good guidance practices serve, I'll talk to you about FDA's process to create a guidance.

Generally speaking, the process for creating a guidance starts with the FDA publishing a draft guidance. What this means is that we publish a notice in the *Federal Register*. The *Federal Register* is the official daily publication for rules, proposed rules, or notices of federal agencies or organizations. It also includes other federal documents, such as executive orders. We then post the draft guidance on the Internet and make it available in hard copy. The notice and the guidance invite the public to comment. Information on how to submit comments will be listed in the notice and also in the guidance.

After a predetermined period of time, which would be mentioned in the notice, we then review the comments and prepare a final version of the guidance, and we make changes as appropriate, sometimes based on the comments that we have received during that comment period.

After the final version is prepared, we publish another notice in the *Federal Register* and post the guidance. Finally,

at that stage, when we have the final version posted, we can implement the guidance.

There's two very important notes on this slide. One, only when finalized does a guidance communicate FDA's current thinking. And second, even though we posted a draft guidance with the specified comment period, the public can still participate on that guidance at any time, even after the announced comment period has closed.

So you may be wondering why I'm talking to you about good guidance practices. What does it mean in relation to the ENDS PMTA draft guidance? Because the ENDS PMTA draft guidance will communicate FDA's policy on a regulatory issue listing the recommendations regarding the PMTA submission, a guidance document is the appropriate way to communicate the information. Therefore, FDA must follow good guidance practices.

Currently, the ENDS PMTA draft guidance is draft, and therefore it is not an FDA-implemented policy. But this guidance, when finalized, will then communicate FDA's recommendations for submitting a premarket tobacco product application for ENDS products and also the general procedures by which FDA intends to review a PMTA.

And this concludes my presentation. Thank you very much.

Carolyn.

(Applause.)

DR. DRESLER: Well, fortunately we have a very full room, so a couple of announcements, please. No seat saving, if the person who you're saving that seat isn't here, they're going to have to find one. So please, no seat saving. And we're working with some FDA personnel, if you want to move towards the back, because we very much want potential applicants to be able to view this. Thank you.

Okay, our next presenter is Caliope Sarago, who will be speaking on Regulatory Overview of a Premarket Tobacco Product Application.

MS. SARAGO: Thank you, Carolyn.

Good morning, my name is Caliope Sarago. I'm a lead Regulatory Health Project Manager in the Office of Science at the Center for Tobacco Products. Today, I will be presenting the regulatory overview for a premarket tobacco product application, otherwise known as a PMTA.

During my presentation, I plan to focus on the marketing pathways and why you would submit a PMTA. Specifically, I will be talking about some definitions, marketing pathways, review phases of a PMTA, Section 910(b)(1) requirements, letters you

may receive from the FDA, organizing a PMTA for submission, meetings with CTP Office of Science, Tobacco Product Master Files, and a brief summary.

The Family Smoking Prevention and Tobacco Control Act was signed into law on June 22nd, 2009 and it amends the Federal Food, Drug, and Cosmetic Act, also known as the FD&C Act, giving FDA authority to regulate the manufacture, distribution, and marketing of tobacco products. Tobacco products are under Chapter 9 of the Federal Food, Drug, and Cosmetic Act.

What is a tobacco product? According to the FD&C Act, a tobacco product is any product made or derived from tobacco intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term "tobacco product" does not include products that are a drug, device, or combination product. Those products are regulated under Chapter 5, not Chapter 9, of the FD&C Act. For example, if an ENDS product is marketed for tobacco cessation or for any other therapeutic purpose, the product will be regulated as a drug or a device rather than a tobacco product under the authorities of FDA's Center for Drug Evaluation and Research, also known as

CDER, or the Center for Devices and Radiological Health, also known as CDRH.

Now that we know what a tobacco product is, what is the definition of a new tobacco product? A new tobacco product is any tobacco product (including those in test markets) that was not commercially marketed in the United States as of February 15, 2007; any modification (including change in design, any component, any part, or 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 where the modified product was commercially marketed in the United States after February 2007.

New products must undergo premarket review and authorization prior to introduction or delivery for introduction into interstate commerce for commercial marketing in the United States.

Why is this important to understand when you have a new tobacco product? The answer is that new products must undergo premarket review and authorization prior to introduction or delivery for introduction into interstate commerce for commercial marketing in the United States.

I will now discuss pathways that are available for

premarket authorization. There are three ways that manufacturers may receive an order from CTP allowing their new tobacco product to be marketed; these are called pathways to market.

The primary pathway for authorization is the Premarket Tobacco Product Application, also known as the PMTA. Application content for a PMTA is described in Section 910(b) of the Federal Food, Drug, and Cosmetic Act.

An alternative to the PMTA pathway is submission of a Substantial Equivalence Report, also known as an SE report. Details regarding this pathway are found under Section 905(j) and Section 910 of the FD&C Act. One important aspect of this pathway is that an SE report requires comparison to a predicate tobacco product.

The remaining pathway is an Exemption from Substantial Equivalence, also known as an Exemption Request. Details regarding this pathway are found in Section 905(j)(3) and under 21 C.F.R. 1107.1.

It is important to understand all three pathways, but as this workshop is focused on electronic nicotine delivery systems, also known as ENDS, I will spend the remaining time discussing which is the most likely pathway, PMTA, for this

product category.

Why submit a PMTA? An order is required for a new tobacco product to be legally marketed in the United States. As previously mentioned, a PMTA is the primary pathway for authorization of a new tobacco product. PMTA does not require comparison to a predicate tobacco product. If you have a new tobacco product in which you do not have a predicate or a comparator product, the PMTA pathway is the best option for authorization.

I will now spend time focusing on how FDA approaches the review of a PMTA so you will have a better understanding regarding how to organize your application.

PMTA contains three main phases prior to authorization. These are the acceptance phase, the filing phase, and the substantive scientific review phase. For a PMTA, a letter regarding a decision will issue at the completion of each phase. As stated in the draft PMTA guidance for ENDS available for comment, a marketing application is considered "submitted" when a complete application is delivered and received by the Center for Tobacco Products' Document Control Center. The review of a PMTA begins with the acceptance phase.

During the acceptance phase, a single discipline reviewer,

typically the Regulatory Health Project Manager, also known as an RHPM, will review the application to determine if basic elements are included for acceptance. Currently, the RHPM will look to ensure that the application is for a tobacco product under FDA's jurisdiction and that environmental considerations are addressed. Later in the workshop, Dr. Gagliano will speak more to environmental considerations.

The next phase is the filing phase. During this phase, a multi-disciplinary set of reviewers performs a threshold review and determines if a substantive review is warranted. The reviewers will look to see if sufficient information has been provided that meet the requirements of Section 910(b(1) of the FD&C Act. I will discuss those requirements in the next slides.

The third phase is the substantive review phase. During this phase, the multi-disciplinary reviewers will be performing substantive scientific and regulatory review of the information provided in a PMTA and will determine if the FDA can issue an order that the new tobacco product may be introduced or delivered for introduction into interstate commerce for commercial marketing in the United States. The additional sessions during this workshop will get into many of the details

that CTP considers during the substantive review phase of a PMTA.

FDA may request additional information about your PMTA as necessary. FDA also may want to inspect your manufacturing, clinical research, or nonclinical research sites to support its review of your PMTA. Additionally, under Section 910(b(2), FDA may refer the PMTA to the Tobacco Product Scientific Advisory Committee, also known as TPSAC, to aid in the review process.

I will now cover the filing criteria of a PMTA under Section 910(b), parts (A) through (F). Section 910(b)1) of the Federal Food, Drug, and Cosmetic Act lays out basic filing requirements for all PMTAs.

Section 910(b)1(A) requires full reports of all information, published or known to, or which should reasonably be known, to the applicant, concerning investigations which have been made to show the health risks of such tobacco products and whether such tobacco products present less risk than other tobacco products. To facilitate review, it is helpful to list any types of publication searches you have performed, and if there are not documents, a statement to that effect.

Section 910(b)1(B) requires a full statement of the

components, ingredients, additives, properties, and of the principle or principles of operation of such tobacco product. Our sessions regarding product science will get into some of the details that our discipline specific reviewers will examine.

Section 910(b(1(C) requires a full description of the methods used in, and the facilities and controls used for, the manufacturing, processing, and when relevant, packing and installation of such tobacco products. Product science will touch on some of the descriptions of methods in later presentations during this workshop.

Section 910(b(1(D) requires an identifying reference to any tobacco product standard under Section 907 which would be applicable to any aspect of such tobacco product, and either adequate information to show that such aspect of such tobacco product fully meets such tobacco product standards or adequate information to justify any deviation from such standard. To facilitate FDA review, if a tobacco product standard does not apply, it is helpful to place a statement to that effect.

Section 910(b(1(E) requires such samples of such tobacco products and of components thereof as the Secretary may reasonably require. As stated in the draft guidance for PMTA,

and currently available for comment, FDA recommends that applicants provide at least one sample of the new finished tobacco product that is the subject of the PMTA as FDA may conduct its own testing and analysis of the new tobacco product and its components and may request a reasonable number of additional samples for testing and analysis. Samples should be submitted to the Southeast Regional Laboratory.

And Section 910(b(1(F) requires specimens of the labeling proposed to be used for such tobacco products as stated in the draft guidance for PMTA on ENDS currently available for comment, the submitted specimens of proposed labeling for all product panels reflect the actual size and color for use with the new tobacco product as part of your PMTA. All labeling you submit also include warning statements appropriate for the product class where applicable, such as the required addiction and recommended nicotine exposure warnings included in an earlier section of the guidance, and should comply with all other applicable labeling requirements under the FD&C Act.

These items are statutory requirements for a PMTA and must be satisfactorily addressed in order to be filed and move on to the substantive review phase. Again, a reminder: The remaining sessions will get into additional details for what is

looked at for both filing and the substantive review phase. I would now like to focus on the types of correspondence you will receive at the close of these phases.

On the previous slides, we discussed a high-level overview of the PMTA review process and shared that after each phase, you will receive a letter from FDA notifying the applicant of the outcome of that phase. I will explain each of these letters in detail now.

For the acceptance phase, as previously mentioned, FDA reviews for acceptance are to determine that the application falls under jurisdiction under Chapter IX and addresses environmental considerations. If these two factors are met, an acknowledgement letter would issue. If these two factors are not met, a Refuse to Accept letter would issue, also known as an RTA. The RTA decision closes all activity for this product. However, an applicant may always resubmit a new application with the missing items.

For the filing phase, currently, FDA reviews for filing are to determine if the applicant met statutory requirements under Section 910(b(1) of the FD&C Act, which we just walked through on the previous slides. If the statutory requirements are met, a filing letter is issued. If statutory requirements

are not met, a Refuse to File letter would issue, also known as an RTF. The RTF decision closes all activity for this product, and the applicant may resubmit a new application with the missing items.

As discussed earlier, during substantive review of the PMTA, FDA will determine the type of order to issue. There are two types: a Marketing Order, which is a final order from FDA stating that the new tobacco product may be introduced or delivered for introduction into interstate commerce for commercial marketing in the United States; or a denial, also known as a No Marketing Order, which is a final order from FDA stating that the new product may not be introduced or delivered for introduction into interstate commerce for commercial marketing in the United States.

In addition to the FDA decisional letters for each phase of review, FDA may also issue letters identifying deficiencies. These letters are known as an Advice/Information Request letter, also known as an A/I letter. Although these are not decisional letters, they do point out issues that FDA considers the applicant needs in order to receive a Marketing Order. These letters may issue in multiple phases of the review phase.

Understanding how FDA reviews a PMTA may help in the

organization for future PMTAs. When thinking about organization, it is helpful to look at the guidance from other centers, such as CDER and CDRH as well as CTP guidances. FDA has a draft guidance on PMTA ENDS that is available for comment. Once finalized, it will represent the Agency's current thinking on what organizational elements to include in an application to better facilitate FDA review.

Organizing a PMTA for submission: As stated in the draft guidance for PMTA ENDS currently available for comment, when organizing a PMTA, it is beneficial to start with a cover letter which may contain basic information identifying the applicant and specific product or products seeking basic information for products seeking a Marketing Order. The cover letter should identify the submission type, for example, PMTA; name and address of the submitter; and additional basic information outlined in the draft guidance for PMTA ENDS. All of these elements will aid in orienting FDA to the purpose of the submission and its content.

Additionally, applicants should focus on an accurate table of contents with working hyperlinks. An accurate table of contents will also facilitate FDA review for quickly identifying all required elements of an application and data to

support them.

As stated in the draft PMTA guidance on ENDS, FDA recommends that the PMTA be well organized, numbered using continuous pagination, be legible and written in the English language. For foreign language documents, the original foreign language document should be provided as well as English translation and certification that the translation into English is accurate.

Also stated in the draft guidance on PMTA for ENDS, you may submit a single premarket submission for multiple products. However, when FDA receives a premarket submission that contains multiple distinct new tobacco products, we intend to consider information on each product as a separate, individual PMTA. Therefore, it is important that clear identification of what content pertains to each distinct tobacco product and show that you have satisfied the requirements of Section 910(b).

For example, if you are submitting multiple e-liquids in a bundled submission, your application should contain information to identify each e-liquid. These e-liquids could differ in name, characterizing flavor, PG/VG ratios, nicotine concentrations. When organizing your submission, you may want to speak with FDA on how to handle and identify information for

each product prior to a submission. It may be helpful to request a pre-PMTA meeting with FDA.

Tobacco manufacturers and importers intending to market products under the premarket tobacco application pathway may request a meeting with FDA regarding research and investigation of tobacco products by submitting a formal meeting request to CTP.

A formal industry meeting with FDA is a forum for the Agency to provide general assistance and guidance to applicants regarding their questions and challenges pertaining to compliance with regulations and requirements regarding the scientific data, information, and discussion needed for FDA to make a final decision on an application. Because these meetings often represent significant opportunities for assistance during the regulatory process, it is important for there to be efficient, consistent procedures for the timely and effective conduct of such meetings.

In July of 2016, CTP issued a guidance entitled "Meetings with Industry and Investigators on the Research and Development of Tobacco Products" to assist persons in determining what to include in a meeting request, how and when to submit a meeting request, and what information is requested prior to the

meeting. This 2016 guidance focuses on tobacco product research and development and is therefore utilized by CTP for application-related meetings. It is available on CTP's website and as a link in this presentation.

CTP has received meeting requests from 2011 to present for various topics, such as questions related to study protocols for consumer perception, nonclinical studies, abuse liability evaluation, and models used to estimate population health impact related to proposed marketing applications. Many of these meetings have resulted in the submission of more complete applications that contain the scientific data, information, and discussion needed in premarket tobacco applications. FDA recommends that a meeting be held well in advance of the planned premarket submission so that the applicant has the opportunity to consider CTP feedback prior to preparing the application and to help ensure the application will be complete at the time of submission and likely to provide the data and information required for the Agency to make a final authorization decision.

Considering the large number of anticipated applications and premarket submission meetings for newly deemed regulated tobacco products, in general, CTP intends to grant meetings for

applicants. This will provide an opportunity for each applicant to receive feedback on their general approach for a complete submission that addresses the scientific requirements of a PMTA.

While meetings are one tool available to help with submission of a PMTA, another tool available is a Tobacco Product Master File, also known as a TPMF.

There may be instances that the applicant does not have all the information to submit to FDA for review of a PMTA. In this situation, the applicant may be able to take advantage of a Tobacco Product Master File. So what exactly is a Tobacco Product Master File?

A Tobacco Product Master File is used to permit the person that owns the TPMF, the TPMF owner, to authorize other persons to rely on information in the TPMF to support a submission to FDA without the TPMF owner having to disclose the information to other persons. These files typically contain trade secrets and/or confidential commercial information that the TPMF owner does not wish to make public.

For example, an e-liquid manufacturer could provide a master file with the chemistry and toxicology data for all the strengths of e-liquid that they manufacture, and a flavorant

manufacturer could do the same for each flavor that they manufacture.

In general terms, the purpose of a Tobacco Product Master File is to allow an applicant to rely on information that the owner does not wish to discuss. FDA, on behalf of the applicant, will assess the information from a TPMF for review of the PMTA.

The next slides will discuss the steps to take to utilize a TPMF. While I am not going to get into the detailed process for how a TPMF is handled, I do want to touch on a few basics.

First, if there is information from another source that you would like to rely upon, contact that source and ask if they currently have a TPMF established with the Center for Tobacco Products. If the answer is yes, ask for a letter of authorization for you to use that information in support of your PMTA. If the answer is no, we recommend that the owner of that information first establish a TPMF with the Center for Tobacco Products and that you also receive a letter of authorization from the owner to reference the information in the TPMF. Once the TPMF is established, the information may then be used to support your PMTA.

One important reminder is that we recommend you always

have a letter of authorization from the owner of the information you wish to reference. If you do not have a letter of authorization, FDA will not be able to look on your behalf in a TPMF to support your PMTA.

So now that you know the basics to establishing a TPMF and receiving a letter of authorization, when does FDA actually review the information?

FDA receives TPMFs and applications at different time points. The deciding factor in the timing of review is the application. If an application contains a letter of authorization to refer to a TPMF, FDA will take the first step in verifying the TPMF can be referenced. Once verified, FDA will conduct scientific review of both the application/submission and the TPMF.

If a TPMF is received and there is no application referencing it, FDA does not conduct a scientific review of a TPMF at the time of its receipt. FDA typically reviews the information in a TPMF only in the context of reviewing a particular submission, for example, when an authorized applicant or manufacturer references material in a TPMF in its application or submission.

Just as a side note, when FDA receives a TPMF, the TPMF

owner will receive a letter establishing that TPMF. Establishment of a TPMF should not be construed as a conclusion regarding its content by the FDA.

To conclude, this presentation covered new tobacco products that may be submitted through the PMTA pathway. It is beneficial for both the applicant and FDA to have submissions organized that answer the basic questions that FDA must go through during the review phases. To aid in a successful submission, additional tools have been provided, such as meetings with Office of Science, guidances, and referencing information an applicant may not own.

The additional talks today and tomorrow will provide additional information regarding the specific content needed to support a Marketing Order for a new tobacco product under PMTAs. If you have additional questions, I encourage you to reach out to your assigned Regulatory Health Project Manager. Your project manager will be able to guide you through the process and aid you in a direction to find information if you need help.

This concludes my presentation. Thank you.

(Applause.)

DR. DRESLER: Okay, our next speaker will be Jeff Smith

presenting a Primer on CTP Electronic Submissions.

MR. SMITH: Thank you, Carolyn, and thank you, Caliope. That was a lot of information, well delivered, well organized. I should give you a moment to absorb all that while I adjust my monitor here.

My name is Jeff Smith. I'm with the Office of Science, Regulatory Informatics. And I'd like to give your brains a rest because I'm here really to make the logistics of putting your submission together and getting it to us as painless as possible, and your focus should be on the content and what's in that submission.

So I'll be covering submission formats and modes of getting it to us, modes of transmission as well as the benefits of electronic submissions and how to prepare for it. And then I'll be talking about something called eSubmitter, which is a TurboTax-like tool you can download to your desktop, which will walk you through the process of filling out the questionnaires and attaching the files and get results in something called an eSubmitter package that you can then submit to us through either the CTP Portal, which was just released in August, to make your life easier, or I'll talk about some other possible ways of getting it to us as well.

And then I'll get into some of the requirements if you do want to use the portal, something called designating Industry Account Manager for your organization who can manage your accounts for your organization.

Two modes of transmission, two modes of submissions. Molecules and electrons, that's pretty much all we have at the present. So paper, we still do accept paper. Electronic submission is preferred, and we found when applicants do this at FDA, they tend to stick with it because it really benefits both sides to have all of your information present, available at your fingertips.

There are several ways you can submit to us. One is through something called a traditional electronic secured gateway that FDA has had available for many years, mostly used by the pharmaceutical industry, but now you can avail yourselves of that mode as well. However, there are challenges with using that. It requires some degree of IT expertise and so on, so it's been a challenge, and we really wanted to make this as easy as possible for you and provide some additional capabilities as well, through the CTP Portal I mentioned earlier.

You can still submit through courier, either on paper or

you could take that eSubmitter package I mentioned earlier, that resulting electronic submission, burn it onto a CD-ROM or other media, and you can still mail that to us.

Some advantages of electronic submissions and submitting electronically are that when you submit to us, the receipt date, the receipt time we get it is the time you sent, and you get confirmation that we've received it immediately. More efficient for us to process, and it could reduce the chance or likelihood of transcription errors because we're going to be receiving the data exactly as you intended to give it to us, so the quality is put into your hands.

More expeditious submission processing and routing, so we get it to all of the reviewers more swiftly, more efficiently, and everything is at their fingertips at all times. The cost of printing and mailing is negligible, I know, and I think we all know next to the cost of putting an application together, but what I can say is the logistics involved in all the label is illuminated, and it makes it a lot easier for both sides to have that information available, and that certainly has some inherent cost savings.

When the submission is mailed, it can take several days to receive it; it goes to a mailing location. That location is

actually available on the web incidentally. I didn't want to put the mailing address in here, but there is a manufacturers' page that lists the address to mail it to. Whether you print it or burn it to CD-ROM and mail it, it goes to that address.

The PMTA guidance under Section 6, I believe it is, references a technical specification that FDA published a number of years ago, and it lays out a list of possible file formats that we're able to process, review, and archive. And you heard earlier about good guidance practices, the regulations. We have to abide by regulations as well as you. Those are our regulations. We also have to abide by regulations on federal recordkeeping, and so we can only really accept submission formats that we can deal with and process and archive down the road.

When you do create an electronic file such as a PDF, we suggest that it's far easier to generate directly from your word processor into PDF format. Anybody that's used the new Word, you can save as PDF, or if you have Adobe installed or other PDF writers, you can generate to PDF. It is far easier and more efficient than printing it out then scanning it back in to make electronic submissions.

When you do scan it back in, if you do have any data or

any images to scan in, ensure that you scan it at a minimum resolution of 300 dots per inch. Make sure that we can view it. If we cannot view it, we cannot review it, and we'll be asking you to resubmit. So that's one way to assure that we can see it and you can see it down the road.

Eliminate any intrinsic inherent security encryption and passwords in the files themselves. The security is in putting it onto a CD-ROM and mailing it to us or using the secure portal and uploading it; that has its own security. When we receive it, it is secure. Putting security constraints on it will only make it difficult for us to use it and would be coming back to you again to resubmit that.

Include tables of contents. The PMTA, under Section 5, listed the requirements for a table of contents. And hyperlinking. Hyperlinking is really more than just a convenience. When you're linking us to a document or a page or a file, without the hyperlink we're having to go and maybe sift through a folder full of files with various filings to try to figure out what it is you're pointing to. So that hyperlink makes it explicitly clear where you want to send us to.

Relative paths is a more technical term. Previously, for many years in the past, we've had problems, FDA has, where if

you're doing hyperlinking, you specify the full path, the folder name, the subfolder name as it existed on your computer. Then when we get it, it's trying to find some folder on your computer. So something called relative paths, to be sure it will work and you don't have this problem.

Best way is to test it. Compile your submission, then put it on a different computer under a different folder structure. Put it somewhere else. If you can open it in that different location, we can probably open it.

Including page numbers will help us in our communications with you and in navigating through the submissions to have those match with the table of contents and any numbering in your narrative, actually printed page numbers rather than just simply depending on the page at the bottom of your status bar, such as Word has a page number even though the printed page number may be different.

There are some instructions on what format and how to save data files. There's a SaS transport format, an open format that many programs can generate into, not just SaS. And there's a specification here which talks about how to do that, such as using the export procedure instead of the CPORT procedure. But earlier, I did list a list of file formats we

can receive, and something called CSV is also available, a comma separated values text file with delimiters that we can also receive that as well as SaS datasets.

Use of lowercase and avoiding special characters. That's a little bit less of a problem now than it used to be, but let's just follow that to be sure that we're not going to have problems.

File extensions, we all understand, help us know what kind of file this is, what program to use to open it. So don't mess with those file extensions.

Use clear, unique file names across your entire submission. If we have to reorganize those files into our systems, we will have duplicate file names based upon different study folders overwriting each other. We want to make sure. Also, that helps us communicate with you what file we're discussing. And there's turnaround of staff on both sides, and as this submission lives into the future, those people will understand what file is what.

So next is how do you prepare for this? You're going to need to do three things. We suggest you download the eSubmitter tool. There is a hyperlink in the next slide. But there are some hyperlinks in these slides, if you do pull them

up. But they both go to the For Industry page and the manufacturers' website page. And if you go to the FDA website, just type in eSubmitter, the top of the find. Even if you go to Google or Yahoo, type eSubmitter. The top return will be the FDA eSubmitter page.

So download that to your desktop. FDA does not know what you have on your desktop. It's going to stay on it just like TurboTax and you own it. As soon as you are ready, you can compile that, save it, and then decide to upload it when you're ready, although it does -- we do have some updates that are needed; we'll add additional features and templates on occasion. So you can run this disconnected from the Internet, but do connect and try to do the updates on occasion.

Create an account. And that's with either the portal, the new portal, or with the electronic secured gateway, so that when you're ready to submit your electronic submission, you have an account to log onto and upload to.

The third is just do it; you're ready to go. And this is not that hard because I had my junior high school daughter do an eSubmitter submission, create one. And you'll be relieved to know that even dumb dads can do it.

So the next thing is to download. Here is a link to

download the eSubmitter submission, but as I said, you can just do eSubmitter search, and you'll pull up this link.

When you do download it and you open it, right now the Center for Tobacco has four templates, but that list will grow; hopefully, we'll have a PMTA one and an SE one, but right now we have the ingredients; the HPHCs; the tobacco health documents and research document submission, you can use it for either; as well as a generic transmittal form which is for everything else. Pretty much you fill out some basic information about who you are, where this is coming from, then you begin to attach your cover letters and such. But this list will grow. Don't be confused when you open it because you'll see other centers have many other kinds of applications or templates.

Then you'll create and you'll save it into a location that you can specify. You have to remember where that location is because when you go to upload it or burn it to a CD-ROM, you're going to want to find it.

Here is an introduction screen to eSubmitter. It looks fairly intuitive. I don't want to get into a training and a review of this, but there's online video tutorials that walks you through it. There's two views. There's an expert view and

a step-by-step view. And when you do create, you'll hit this where it says create new submission, where my cursor is, and you'll have several templates to choose from. You'll select those, then you walk through filling out information, contact information and such. It even lets you save contact information so that you can reuse it for future submissions, less to fill out in the future.

Then you begin to attach files. Here's a page here, and you would click the plus button and up -- would pop up something. I'm going to attach a cover letter, so I'm going to browse to wherever you chose to hide your cover letters on your computer, then you select it and attach it. And it really is that simple. Just be sure those documents are legible and searchable.

And the last step is to package it. Packaging really is just it goes through a check to make sure you fill out all the information you need and any attachments you have, if there are required attachments. In more sophisticated templates it will say you didn't attach this or you didn't attach that. And then it will compile it into a zip file, a compressed zip file, then you can take that zip file, and that's your submission.

You do not need eSubmitter to open it up and review it.

At that point you can be outside of eSubmitter; that zip file is what you need, just like you don't need 2012 TurboTax to open up 2012 returns. You've probably saved it as a PDF. That's what you use to view that old return. So you could also specify down near the bottom here where it is you want to save it because you're going to have to find that when you eventually go into the portal and want to upload and send it to us.

CTP Portal is the newest way to submit. We just released that August 8th, and we've already received over 100 requests for accounts, and we've received a number of submissions. The count is going up, but the first month we received I believe it was about five submissions, and three of those were from companies that had never submitted, period. One of those was from a company who had submitted on paper only, previously. So they did find it a lot -- much easier, from our feedback from our pilot. You do not need to establish this electronic secure gateway account. And I'm not going to get into the details, but you can find information about that electronic secure gateway online if you do choose to do that.

Some companies do submit pharmaceutical-type products as well as tobacco-type products, and they stay with the gateway.

But you can just stick with the portal, if you wish. You'll see your submission after you upload it, and you'll see what the status is, and the portal also allows you to see information about each submission, such as what is the STN, what is the submission tracking number, STN, that's been assigned, what is the administrative status of that.

You will not be able to get in and see the content of the electronic submissions, but anybody in your company who your Industry Account Manager has given access to would be able to see administrative information about what was submitted and when, but they won't be able to open up and view the content of it. Whether that IAM gives everybody who has an account that access or not is up to your company really and your IAM.

It allows for messaging back and forth between your company and us, much like an HMO has a website where you can log in and you have a secure portal, you can communicate with your doctor in a secure way. This does the same. However, I do need to mention that in this phase, we're not initiating communications from the industry yet. You'll still have to call up, communicate with your RHPM or with the FDA. They can open a thread, and you can begin communicating through that e-mail thread online, and that's at the current time because

this is new.

You will need to assign an Industry Account Manager, and that is, I believe, after this set of slides here.

So this is the home screen, the landing page of the portal. The link is on the lower left. You can also find this, again, like the other -- like the address to where to mail it on the manufacturers' site. So after you log in, across the top you will always see a menu across the top, and one of these bars, buttons on the right side, very pronounced, says Launch Upload Tool. So you've created an eSubmitter submission, attached your cover letter, saved as a zip file somewhere. Now you're in the portal. All you have to do is click upload, and it's going to ask you to find the file, upload it, say a few things about it.

An Industry Account Manager is your gatekeeper. Your company best knows who within your organization should have an account and that's -- we're very serious about security and confidentiality. We want to put that role into your hands. So you'll designate through a process of submitting a letter to us that I'll get into; an Industry Account Manager, they will decide whether it's just going to be them to communicate with us, or should they create subaccounts for their organization,

and they can assign roles and what they can view in the subaccounts.

It needs to be an authorized individual, and if you're a company representing a manufacturer, you have to have the actual manufacturer cosign that because these accounts are for the manufacturers; each manufacturer has one. So you'll be a representative going into that company's account.

So provide us the contact information on company letterhead. It should be signed by a responsible party of that organization. And just to reiterate, third party representative of a manufacturer, you also have to have that manufacturer sign as well.

Secondly, just like all federal -- federal employees have to assign Rules of Behavior and such, so this is a system, it has some information in it, we want to be sure that you understand this and that you agree to this and know what you're responsible for, so you'll have to sign that, Rules of Behavior. Then mail it to the address I mentioned in the manufacturers' site. The manufacturer has these instructions and the examples of Rules of Behavior.

So we've reached the end. So thank you very much, and we hope to see your submissions soon. And any questions, there's

an e-mail address here and a phone number. Now, questions we receive are not of regulatory nature. If we do receive questions in a regulatory or policy nature, we will refer it to the RHPM or refer you to the earlier presentation that Caliope talked about where there's a procedure for meetings with industry, so we're going to try to keep any questions that we entertain as technical and logistical and administrative as possible so we can quickly resolve these issues of you getting your submission to us in a timely manner.

Thank you very much.

(Applause.)

DR. DRESLER: Okay, our next presenter, and then following this presentation, we'll have the panel and answer some questions. So Dr. Kimberly Lindsey, the Concept of Bridging Information.

DR. LINDSEY: Thank you, Dr. Dresler.

And again, I say good morning to you. I am a medical officer in the Office of Science, Division of Individual Health Sciences, Center for Tobacco Products. My name is Kimberly Lindsey. And I will be briefly introducing you to the topic or the concept of bridging information.

I will cover the following sections in my presentation:

what is bridging; the importance of bridging studies; when to consider a bridging study; main concepts for applying bridging; and then I will finally conclude with a few generic examples.

I want to emphasize, however, that although I will be introducing the concept of bridging, and I'll cite some general examples and principles that pertain to bridging, you will hear about more discipline-specific examples of bridging in subsequent talks over the next day and a half or so.

So what is bridging? Well, the concept of bridging actually took foothold in the 1990s during a time when pharmaceutical industries were expanding their markets globally, and it culminated in a series of International Conference on Harmonisation guidance documents, which I'll just call short, ICH documents. And according to these guidelines, a bridging study on a product can be defined as a supplemental study performed in a new region to provide pharmacodynamic, that is, what a chemical does to the body, or clinical data on efficacy, safety, dosage, and dose regimens in a new region that will allow extrapolation of the foreign clinical data or the new clinical data to a new region.

So in other words, a bridging study is an additional study on a product that is performed in a new population to build a

bridge between the information that is already available from tests already done and then questions that are arising from the regulatory body. And those regulatory questions vary. They could be related to ethnic factors or to product characteristics, and we'll provide a few more examples in the next few slides.

Therefore, not only can bridging apply to clinical information in the way of populations, but it can also apply to product characteristics. So along these lines, guidance was also issued pertaining to drug product as it pertains to a manufacturing process, and hence that brings us to the second bullet, a study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from a drug product or chemical produced on a current process, and it compares that, then, to a changed process. And we're going to be repeating this theme throughout, but we're going to state it in multiple ways, so hopefully it will start to sink in. So it's not a very easy concept to necessarily get.

Bridging studies, as you can see, take comparability into account. When there are differences in comparability, then a bridging study or bridging information is used to explain those differences and provide additional information if there is some

uncertainty regarding whether the differences will impact the statutory requirements for authorization on whatever regulatory question you are attempting to answer or address.

It also saves duplication of effort because you're using existing available data and only the new tests that are necessary for the new conditions. Bridging is commonly used to verify product characteristics through comparability, that is, a side-by-side comparison of products or sets of data. But the ultimate goal is to use the existing information, be it clinical, nonclinical, or product information for an original product and then apply this information to the new product.

Now, historically, bridging has been used to extrapolate to new or different regions. For example, a product that's developed outside the United States is now being planned for marketing in the U.S., so we'd be doing a comparison on a variety of parameters. It could be done when it comes to age groups -- youth versus older people -- a new demographic, or it could be a change in a manufacturing process, it could be a change in a device design.

But essentially, the bridging studies demonstrate a link between the completed studies and the new information as well as providing any explanation for gaps in that information.

Bridging studies, as you can probably guess, are fairly common in the pharmaceutical industry, and many FDA and ICH guidance documents actually mention bridging studies as a way to provide information for various types of products. And, in fact, the draft guidance for industry, the PMTA for Electronic Nicotine Delivery Systems, available for comment, states, "If an application includes, for example, information (published literature or marketing information) with appropriate bridging studies, FDA will review that information to determine whether it is valid scientific evidence sufficient to" support or "demonstrate that a product is appropriate for the protection of public health." So that term "bridging studies" does apply here.

So when might you consider a bridging study? Well, in summary, there are some general situations when a bridging study may be considered. For example, I mentioned before if you're comparing different populations, and I mentioned age, could be gender, could be ethnicity, or based on some kind of medical condition; when comparing a new product to a reference product, and there is a need to show that there are some similarities and differences between the products.

Generally speaking, a regulatory application could include

studies conducted using the actual new product; however, bridging of data from one product to another may be feasible for a subset of products or certain types of studies. For example, it's common to apply pharmacologic studies as bridging studies where a product has the same or a different dose response, or perhaps there is a different concentration of a product.

And to this point, the PMTA ENDS guidance, available for comment, cites the following example: If you have, say, some X flavor of e-liquids with nicotine concentrations that are ranging from 1 mg/mL to say 24 mg/L, that may not require unique studies for each nicotine concentration of the X flavor product if data from a subset of nicotine concentrations, for example, low, middle, or high, of the X flavor products may be bridged or linked to other concentrations of the X flavor products.

And finally, it may be possible to use bridging if there is a need to show relative risks and benefits between two products.

Now, there are some main principles for applying bridging studies. They are used to explain why the data are applicable to the new product. There should be a clear rationale and

justification to support bridging to allow FDA to assess whether the findings of such studies would be relevant to the product that is the subject of the application. As a general principle, the methods for identifying and evaluating evidence should be transparent. And if the literature is used for bridging, it is important to extrapolate the extent to which the findings of available literature may or may not be generalizable to the new product. And finally, there should be an unbiased assessment of the available information, taking into consideration both the positive and the negative information available.

On a previous slide, I mentioned literature, and often literature reviews in lieu of clinical trial data are used to provide bridging information. However, it's important to bear in mind that there are some potential limitations of a literature approach to bridging.

Studies in peer-reviewed literature often do not include study protocols, analysis plans, or detailed study reports, and often the original data are not available for review and analysis.

Second, peer-reviewed literature may not fully describe the methodologies used in the design and the analysis of the

reviewed studies and may not fully assess the validity of the reported findings. And hence, these factors may hinder the ability to draw solid conclusions.

Now, I'm going to conclude the presentation with a few generic examples of how bridging studies are applied. With regard to chemistry and manufacturing, bridging studies are also commonly performed when there is a modification made to the manufacturing level with regard to its preparation, its packaging, storage, or dosage, or other changes that might affect the product composition or performance or the delivery of the product to the end user.

As you heard earlier this morning during the regulatory overview of PMTAs given by Caliope Sarago, the Substantial Equivalence pathway is one pathway to market a new tobacco product. PMTA and SE have different standards of product authorization, but an important aspect of SE is that this pathway requires a comparison to a predicate tobacco product.

There are some concepts of SE, however, that may be applicable within the context of a PMTA submission considering how the information pertaining to a specific product may be relevant to the proposed PMTA product. And I'll provide you three examples from the SE.

What is the description of composition, explaining how the design, material, ingredients, and heating source of the product are integrated to produce the final product. And if the new tobacco product differs from its eligible predicate, then that description should contain enough detail to demonstrate that the change in the composition does not raise different questions of public health. And this is an example, this is the regulatory question that needs to be addressed, and you need to provide the information to link that information. Bridging studies are one way to address whether the comparative differences between the predicate and the new product raise different questions to public health.

Another example from SE would be the listing of harmful or potentially harmful constituents. Again, this is a comparator, a comparison of side-by-side new product versus the predicate. And in this example for tobacco products that are smoked, report the comparative quantitative levels of smoke using both the International Organization for Standardization, or ISO, and the Canadian Intense smoking regimens.

But in keeping with the concept of bridging, if an alternative method is used, you need to explain and bridge the gaps. So how does the alternative regimen provide comparable

results to the ISO and Canadian Intense regimens?

And the third example: description of the heating source (example, burning coal, electric, chemical reaction, carbon tip) used in the consumption of the finished tobacco product. If the heating source of the new tobacco product differs from its eligible predicate, the description should contain enough detail to demonstrate that the change in the heating source does not raise different questions of public health. So these are just a few examples here from SE.

Now, just move into some clinical examples. When it comes to pharmacokinetic data, this is probably one area we -- you almost may consider this to be sort of a classic type of situation where you use bridging studies. But clinical data that provide information about how a chemical is handled by the body is what we refer to as PK.

So that includes how the chemical is absorbed, how it's distributed, how it's metabolized, and how it's excreted in the body. Those could include measurements of blood concentrations of the chemical and its breakdown of products or metabolites at regular intervals after it's ingested.

Another example would be pharmacodynamic data which gives information on what the chemical does to the body. And these

data include dose-response relationships, and they describe the physiological effect of a chemical at different doses or concentrations. So these bridging studies could be done with these kinds of data to assess the toxicity of a new product or compare the bioavailability, which is the proportion of a chemical that enters the circulation when it is introduced into the body and is able to have some active effect. Or it could be a measurement of the rate or the extent to which a chemical reaches the site of action.

Now, there are some situations for using nonclinical bridging data, and in this context, by nonclinical, I'm talking about nonhuman data to bridge gaps. And this typically would be, again, related to pharmacodynamic or pharmacokinetic information regarding response, toxicity, etc.

But sometimes those things are not adequately characterized, and if the previous characterizations were not conducted in a new population, or they didn't comply with local regulatory requirements or didn't comply with good clinical practices accepted by the new region or the regulatory body that you're seeking to market your product in, or they didn't use appropriate endpoints for assessing the product, then it might be a situation where you might want to use nonclinical

data for bridging gaps.

Bridging can also apply to assessing potential health risks, for example, looking across products to assess behaviors. For example, if there's publicly available data on the use behavior of some Product X and an applicant wants to use that study to support likely use behavior of the proposed product, then providing bridging information between those two products might help support the rationale for being able to use that study and Product X.

You could also use it when evaluating different populations in terms of whether they are experienced/inexperienced users, or based on their use of the product, could be single versus dual versus poly use of products, taking into consideration situational uses of the product and possibly even design features and marketing. And I'll reiterate that although I'm providing some general examples, you will be afforded the opportunity to get more specific examples based on various disciplines in subsequent talks.

And finally, in concluding the clinical examples, while bridging a new product to existing data is an option, there may be some circumstances when a bridging study could be conducted

such as when a product is sensitive to intrinsic factors. What do I mean by that? When a product is likely to act or change in a way depending on your gender, your race, age, or some underlying physical condition. Or it could be that it's sensitive to some intrinsic factors. What do I mean by that? Some environmental factors that you can't change, perhaps some cultural factors that need to be considered.

So if those are likely to change, or there's a possibility that those could change depending on your gender, your race, age, pathology, it may be necessary to do a supplemental study. On the other hand, if the product is not sensitive or insensitive to these factors, then it is possible that a bridging study may not be necessary.

And with that, I conclude my presentation on bridging concepts. I thank you very much for your attention.

(Applause.)

DR. DRESLER: Could we have the presenters come up to the front, panel, please? Okay, so we're going to have some questions and answers now for about 15 minutes before our next break, or our first break. Again, let me reiterate, we're not going to answer any company-specific or product-specific question or questions of policy, but more these are clarifying

questions from these presentations. I have some questions that came in online prior to today which I have to ask, but also if you have questions in the room, please write them on the cards that are available. We have volunteers that are passing out these white index cards. And if you are online, please do send them in to the website, and we'll get those questions asked.

So as we're getting some questions from the room and online, let me start out with one of the ones that came in online.

Multiple preclinical and clinical trials will be required for each PMTA. The firm I represent will be requesting a meeting face-to-face in order to share our study designs and objectives with the FDA to ensure that the design strategies are in line with FDA expectations. Will the FDA accommodate our meeting request with a favorable meeting time within 60 days from the receipt of a meeting request?

Caliope, do you want to address that?

MS. SARAGO: CTP has performance goals to responding to requests for meetings. We recommend that you submit a meeting information package at least 45 days, and we must respond to your request within 21 days, calendar days, prior to scheduling the meeting. The process for requesting a meeting I went over

in my presentation and provided a link to the FDA's guidance, "Meetings with Industry and Investigators on the Research and Development of Tobacco Products." And that can also be found on our FDA website.

DR. DRESLER: Okay. The FDA said it identified at least one predicate product. Can the FDA please state what the name of that predicate product is?

MS. SARAGO: The burden of identifying a predicate product is that of the applicant's. However, for submission for a premarket tobacco application, as I mentioned also in my presentation, you do not need to have a predicate for submission of a PMTA.

DR. DRESLER: Okay. After a PMTA is approved for market, will then that product become available to other manufacturers for use in their applications?

MS. SARAGO: As a general rule, tobacco products are not approved but receive Marketing Orders. And as I also mentioned in my presentation, you have available to you to use a Tobacco Product Master File if you would like to reference information. We do recommend that you get a letter of authorization prior to requesting review of that TPMF.

DR. DRESLER: I think this one's coming for you, too,

Caliope. What is the current timing for setting up meetings relating to scientific advice for a PMTA? From the time for the request to the meeting date, what is that timing?

MS. SARAGO: We have to respond within 21 calendar days, and we'll send a letter either requesting or denying the meeting, and we recommend that you look at the guidance for industry for details on what to submit to ensure your meeting is approved.

DR. DRESLER: Okay, what are the -- Caliope, I'm sorry -- time estimates for the various acceptance filing review phases? What are those timing estimates?

MS. SARAGO: Our acceptance, if an application is accepted, the applicant will receive a letter of acknowledgement acknowledging receipt of that application. If an application is refused to be filed, they will receive a Refuse to File letter upon receipt of that information.

DR. DRESLER: Okay. When will all of these regulations begin to take place?

MS. SARAGO: The deeming rule went into effect on August 8th of 2016. Currently, we have the guidance for ENDS that is available for comment that can be referenced.

DR. DRESLER: I think I'm just going to be staying with

you, Caliope. With each flavor, we offer zero nicotine or levels of, say, 0.3, 0.9, 1.2, and we offer five sizes, so each size and nicotine levels will need its own PMTA; is that correct?

MS. SARAGO: So yes. An applicant may bundle applications for multiple distinct products into a single submission, as I mentioned. However, as separate determinations are made on each distinct product, FDA will unbundle these submissions, and we will make determinations based on each separate application. The applicant is responsible for providing data that supports each of the distinct products that they are submitting.

DR. DRESLER: Jeff, can the CTP portal be used to submit Tobacco Product Master Files?

MR. SMITH: Give you a rest.

Yes, it can through the general template, the generic template using eSubmitter. So everything -- if you're going to submit through the portal or ESG, you need to use an eSubmitter tool to save and package your file, and just select the generic template at the moment and fill the information out, then attach your associated data and documents.

DR. DRESLER: Okay. How about another one? Can a PMTA form be populated progressively as a company compiles its

supporting product information?

(Off microphone response.)

MR. SMITH: Press 1, 2. Okay.

eSubmitter, for those applications that we do have templates for, and more are to come, for those applications that we request lists of data, line items of data, we provide in the eSubmitter tool an Excel spreadsheet, which is a template, that you can then take out of eSubmitter and populate it.

I imagine you can generate some scripting to populate those data, and then you can input them back into eSubmitter. So that should give you some middle where -- some way to do that. ESG also, as we develop new standards for electronic submissions in the direction the rest -- FDA has gone with the electronic common technical document, more sophisticated standards will come about where you can build it on your own and submit it using certain data standards, but that's down the road.

MS. SARAGO: I'd also like to add that currently PMTA does not have a specific form that you can populate with your submission.

DR. DRESLER: Dr. Lindsey, so this is about bridging. For

medicines, the criteria for bioequivalence are established, for example, PK parameters within a certain band, but there seems to be a more open or flexible definition to bridging for tobacco products. Do you expect CTP to move towards more explicit criteria?

DR. LINDSEY: Yes. Let me just move this. Can you hear me in the back?

Right now, I can't answer that question for you. The best thing for people who are considering using bridging studies is to discuss with us your specific situation either by asking, sending something to AskCTP@fda.hhs.gov or requesting a meeting as per the information that was given to you by Caliope Sarago. But at this time, I cannot answer that question.

DR. DRESLER: Caliope, we're coming back to you for a more explicit answer than before. If a meeting is requested tomorrow, when might the applicant expect to meet with FDA? So if asked now, when will the meeting be likely to happen?

MS. SARAGO: That would depend on the type of meeting that you're requesting. That would also depend on the information that you admitted to discuss and -- but we would respond to you within 21 days, whether or not we are granting or denying the meeting. Also, availability of our review team that would need

to review the meeting and the information, the size of the package that you would send, all of that is a determination in when the -- also your availability, for industry. All of those are determined or determinations in when we would be able to schedule.

DR. DRESLER: Okay. And then I'm going to take some answers here.

So what determines the applicability of a tobacco product standard? In particular, what status/standing of a product standard must it have? And so I would respond to that. Currently, FDA and the Center for Tobacco Products has no product standards. We encourage you to monitor the website for updates because that will be worked on.

(Off microphone comment.)

DR. DRESLER: Characterizing flavors is a product standard, okay. So all right, thank you.

And then another question. Some longer-term studies, such as stability studies, may produce final data after August 8th, 2018. How will an applicant add data to an application after it has been accepted and filed?

MS. SARAGO: If an application is accepted and filed, an applicant may submit an amendment to that application.

DR. DRESLER: Okay. All right, any other questions? Get them in on the cards. I have a couple more that came in from previous.

Will there be an online submission form for a PMTA?

MS. SARAGO: As I previously mentioned, currently there's no online form for a submission of a PMTA.

DR. DRESLER: Will FDA release a flowchart of activities and steps that small companies must undertake to successfully prepare their material for a PMTA?

MS. SARAGO: The information that was presented in my presentation and also that went over content and format should be helpful, also review of the PMTA and guidance. Those are tools that you can use.

DR. DRESLER: Okay. I don't see any other cards coming up. Any -- and those would have included the ones from online. And we're actually 1 minute ahead of schedule, so how bad is that?

Okay, so we're going to take a 15-minute break. You heard where the bathrooms are, down the hall to the right, or upstairs to the kiosk for some coffee or a snack. Be back here -- we'll start at 10:30 promptly. Thank you.

(Off the record at 10:14 a.m.)

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

DR. DRESLER: Dale, do you see people out in the hallway that you can say come on in? Thank you. And while they're coming in, let me go ahead and address a question that came in online that missed the last session, so let me ask the question, and then I'm going to answer it, too.

If the owner of the TPMF refuses to allow permission to reference their Tobacco Product Master File when requested by a second manufacturer, you said to include a copy of the letter of the request. Not quite. You need to include the letter of authorization allowing you, the second manufacturer, to reference their TPMF. Okay, so just ask them and they said no isn't good enough. You got to get their letter of authorization and include that, okay?

Okay, people are still filtering in. We're going to go on to our second session for the day. And this is on Product Science Overview. So for all of you science geeks, this is the session for you, the exciting science.

So our first presentation is Chemistry of ENDS Products, and this will be given by Dr. Tianrong, who is a chemist within our Division of Product Science. Tian.

DR. CHENG: This is Tianrong Cheng. I'm a chemist from

Division of Product Science, Office of Science in Center for Tobacco Product. And this presentation focuses on the chemistry of ENDS products, the chemistry information that may be helpful for understanding the ENDS product from a science perspective.

This presentation goes through the chemistry information relevant to ENDS products, using final guidance and draft guidances as examples. The final guidance includes the HPHC final guidance, the SE final guidance, the listing of ingredients final guidance, and the Tobacco Product Master Files final guidance. And the draft guidance includes the reporting HPHC guidance and the draft guidance on PMTAs for ENDS, which is available for comment. The chemistry information includes that of the ingredients, the additives, the constituents, the collection and analysis of constituents, and product stability.

This presentation also provides the definition for additives, constituents, the proposed list for HPHCs and other toxins as appropriate, and also references and links to the documents used in this presentation.

The definition for the constituents and the additives may provide help for understanding this presentation. They are

definitions by the statute and by the final guidance. The chemistry relevant key words are underlined.

By definition, additives are any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substance intended for use as a flavoring or coloring or producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding).

Smoke constituents, by definition, are any chemical or chemical compound in mainstream or sidestream tobacco smoke that either transfers from any component of the cigarette to the smoke or that is formed by the combustion or heating of tobacco, additives, or other component of the tobacco product.

HPHC final guidance defines harmful and potentially harmful constituents. They are the constituents that is, or potentially is, inhaled, ingested, or absorbed into the body, including as an aerosol or any other emission, and causes or has the potential to cause direct or indirect harm to users or nonusers of tobacco products.

Overview of the ENDS products identify areas that are chemistry relevant, includes e-liquids and aerosols. E-liquids

contain ingredients (intended or unintended), additives, and reaction products. Aerosols are generated from e-liquids and a functioning aerosolizing apparatus. Aerosol contains constituents. Constituent testing may provide health risk information for the new product.

Intended ingredients in the additives are those that are intended to be used by the manufacturer in the tobacco product. Ingredients could be tobacco, substances, compounds, and additives. The supplier of the ingredients may have the ingredient information, for example, the quality of the ingredient and the identity of the ingredient. The product designer and manufacturers may have the ingredient information, for example, the location of the ingredient in the tobacco product, the quality of the ingredient, the expected function of the ingredient, and the quality specification of the ingredients in the product.

The owners of the information could put this information into Tobacco Product Master Files which can be used by other manufacturers who use this product in the making of a new tobacco product. As Caliope discussed in her slide, Tobacco Product Master Files may be helpful for ingredient information submission by obtaining authorization from a master file owner

and by referencing master file for information on ingredients, materials, and composition.

Helpful ingredient and additive information includes the identification of the tobacco product manufacturer, the identification of the tobacco product importer, and the identification of the tobacco product itself. It also includes the ingredient location, where the ingredient was added in the tobacco product; for example, it could be in a component, in a subcomponent, or in the material used for the tobacco product. It includes the unique identification information of the ingredients.

For ingredients that have a single chemical substance, unique identification information of the ingredient includes the identity of the ingredient, for example, name, common name, and CAS number; the quality of the ingredient, for example, the purity and the grade of the ingredient; the quantity and the unit of measure of the ingredient; and the expected functions of the ingredient in the tobacco product.

For ingredient/additives which is a complex purchased ingredient, distinguish between that made to the manufacturer specification and that is not.

For complex ingredient that is made to the manufacturer

specification, unique identification information for each individual ingredient in the complex ingredient, the identity of the complex ingredient, and the identity of the supplier or manufacturer of the ingredients may provide helpful information to identify the complex ingredients.

For complex ingredient that is not made to the manufacturer specification, the identity of the manufacturer or supplier of the ingredient, the identity of the complex ingredient, the quality and expected function of the ingredient may help.

Reaction products may also be considered as ingredients. They are the substances known or tend to be formed during tobacco product manufacturing and storage. Helpful chemistry information for the reaction products is the same as those for the intended ingredients/additives. They include unique identification information of the reaction products plus the source information of the reaction products.

One example of the reaction products in ENDS products is the potential nicotine N-oxide formation due to the nicotine degradation/oxidation in e-liquids during the manufacturing of the final product, as Etter's and Flora's publication reported.

Unintended ingredients/additives are those that are added

unintentionally. Examples are, for example, nicotine-related tobacco alkaloids were found to be in the e-liquids and added to the e-liquid with nicotine. Propylene glycol/vegetable glycerin related to diethylene glycol was also found in the e-liquid and was found to be added to the e-liquid with the carrier solvent.

Metal, for example, arsenic was also found in e-liquid. Metal may be added into the e-liquid through the interaction between the tobacco product and the processing equipment, the closure/containment systems, and may also be present in the tobacco component.

Constituents may include HPHCs and other toxins as appropriate. Examples for HPHCs include the toxicants, carcinogens, addictive chemicals in the chemical compound that have the potential to cause direct harm to users or nonusers of tobacco products. They also include the chemicals that have the potential to cause indirect harm to users or nonusers of tobacco products.

Other toxins as appropriate may include toxins the ENDS contain or are present or emit. Examples are diacetyl, as Allen's work reported, and diethylene glycol, as published in McAuley's and Westenberger's work.

This slide provides the proposed list of HPHCs and other toxins as appropriate in draft guidance on PMTAs for ENDS, which is available for comment.

Aerosol generation collects constituents for further qualitative or quantitative analysis, utilizing operating condition range and use patterns likely to be used by the user; when used in new products, a reasonable range of e-liquids or devices likely to be used by the user in conjunction with a new tobacco product. May help to generate reflective likely range of delivery of emission from the new product and to compare to other products on the market, for example, other ENDS products or combusted cigarettes.

Complete description of the aerosol collection method and the aerosol generation machine information may provide help in understanding of the aerosol generation process.

Product (intended) use conditions for likely range of delivery of emissions includes the intense condition and non-intense condition. Intense condition generates higher levels of exposure when set, for example, at higher coil temperature or at higher voltage/wattage settings and with heavy use pattern. Non-intense condition generates lower levels of exposure when set at lower settings or with lower setting

systems, for example, e-cigalikes and other typical/light use pattern.

Analytical testing collects qualitative or quantitative constituent information. Summary of testing, full testing information, and the method of measuring and references may provide helpful information for understanding the analytical testing.

Summary of testing and full testing information includes the information for the constituent: constituent name and the CAS number; the unit of measure of the constituent, for example, the unit of mass per unit of use or per unit of mass; the measure of the mean values with 95% confidence intervals; and the number of replicates. For example, the reporting HPHC draft guidance proposes 7 to 20 replicates for combustible tobacco products, and the draft guidance on PMTAs for ENDS, which is available for comment, proposes 10 replicates per batch, minimum 3 batches for ENDS products. It also includes the dates of testing and dates of manufacturing.

Method of measuring and references include the test methodology; the test procedures, for example, the standard operation procedures for extraction, separation, and detection; and the rationale for selecting the method.

Data comparison may be helpful when compared with other tobacco products for potential health risk reduction and with other similar tobacco products for potential product switching.

Quality of analytical testing may provide information for the accuracy and representation of the constituent information. The information regarding the analytical data quality includes the test laboratory accreditation status and the scope; the method validation status, for example, the validation for accuracy, precision, specificity, reproducibility, limit of quantification, linearity and range, system suitability, and robustness of the method -- ICH guideline for validation of analytical procedure Q2(R1) is an example; and also the representativeness of the test products.

Formulation verification may also involve chemistry testing. Verification information includes e-liquid formulation stated for the product properties, whether the manufacturing specifications were met, and if available, applicable authorization to the reference from the master file owner to reference the supplier's Tobacco Product Master File.

The product stability may be defined by the product's shelf life and the product's lifetime and may determine the storage condition for the tobacco products. Information

regarding the product's shelf life includes how shelf life is determined and the factors that determine the shelf life, for example, volume of e-liquid. Information regarding the product's lifetime includes the description of the lifespan of the product and the consistency and the stability over the product's lifetime. Information regarding the storage condition for the tobacco product includes how stability may be affected by storage conditions: for example, the moisture and the temperature; and the chemistry changes, for example, in pH and the constituents over the lifespan of the products.

The last two slides, Slides 12 and 13, provide the references and links to the documents used in this presentation. They include the final guidance, the draft guidance, the deeming rule, the statute, the ICH guidelines, and the scientific publications cited.

Thank you very much.

(Applause.)

DR. DRESLER: Thank you, Tian.

Our next presenter will be Komal Singh, who is an engineer and will be speaking on Engineering Considerations for ENDS Products.

MS. SINGH: Good morning. My name is Komal Singh, and I'm

an engineer in the Division of Product Science in the Office of Science. I'll be discussing the general engineering principles for ENDS products. Today I will be reviewing the PMTA statutory requirement and definitions, the basic principles of product design, product operation, and product manufacturing.

First with the PMTA statutory requirement and definitions: From the FD&C Act, engineering evaluates complete characterization of the products based on the components and properties; the principles of operation; and the methods, facilities, controls for manufacturing, processing, and applicable packaging.

Some of these definitions for these terms can be found in the final deeming rule. When we say component or part, we mean any software or assembly of materials intended or reasonably expected to alter or affect the tobacco product's performance, composition, constituents, or characteristics, or to be used with or for the human consumption of a tobacco product.

A component or part excludes anything that is an accessory of a tobacco product. Some ENDS component examples are e-liquids, atomizers, batteries, cartomizers, and programmable software, whereas an accessory is any product that is used with a tobacco product, and it does not contain tobacco and does not

alter or affect the tobacco product's performance, composition, constituents, or characteristics, or is intended to affect or maintain the tobacco product's performance, composition, constituents, or characteristics, but it does solely control the moisture and/or temperature of the stored product or provides an external heat source to initiate combustion of a tobacco product. Some accessory examples include screwdrivers or lanyards.

Product characterization generally includes product analyses and testing and product properties.

As stated in the draft guidance for PMTAs on ENDS, which is available for comment, a full statement of product analyses and testing includes identification and complete characterization of the components, properties, ingredients, additives, and principles of operation.

And the properties include a full description of the product dimensions and overall construction of the product, design parameters, performance specifications, and a comparison to currently marketed products in the same category. For example, if your PMTA is for an e-liquid, it would be helpful to compare other e-liquids with similar nicotine content, flavors, and other ingredients used in the same manner and

under similar conditions.

Because it is expected that consumers of current products that are of the same category may switch to using a newly marketed product, it is important that FDA be able to evaluate whether the switching would result in a lower or higher public health risk. Dr. Chen will discuss this further later in the workshop.

Now, to go further in detail about the different engineering statutory requirements laid out in the Act, the engineering analysis for the first part of 910(b)(1)(B) focuses on the basic principles of product design, which are primarily the design parameters that characterize the product.

A design parameter describes what specifications the product is manufactured to in order to characterize the product, and it is identified by a target specification, upper and lower range limits, and test data, where a target specification provides the exact manufacturing standard to which a design parameter must conform, and it is typically identified by a single value. The range limit characterizes the product based on the target specifications and product attributes and is typically identified by a lower value and upper value in the same units as the target specification. For

example, a target specification for resistance would be 0.5 ohms whereas the 3-inch limits would be 0.45 to 0.55 ohms.

Test data confirms that the product meets the target specifications and falls within the acceptance criteria and is identified by a protocol, acceptance criteria, dataset and a summary of results, where the acceptance criteria are based on and determined after the target specifications and range limits are established and demonstrate whether the product conforms to the standards. And a dataset typically spans multiple batches with multiple replicates. Validation and lab accreditation information would also be helpful to characterize the methods.

An example of the product design evaluation can be found in the Swedish Match North America PMTA, who received a Marketing Order. Even though it was for smokeless products, the general engineering principles still apply. The engineering analysis included the characterization of the snus tobacco design parameters and the pouch design parameters. It also included a comparison to other snus products that were on the market, FDA laboratory testing to verify product design, and evaluation of standards used from ISO and CORESTA.

The draft guidance on PMTAs for ENDS includes a non-exhaustive list of examples of ENDS design parameters:

For e-liquids, volume, viscosity, and boiling temperature provide characterizing information to allow for an engineering evaluation.

For the wick, the parameters include the amount of wicking material, which is the mass and grams of the wicking material; the wicking rate, which is the rate at which the e-liquid travels through the wick; and the ignition temperature, which is the temperature at which the dry wick will combust.

For the coil, the parameters include the coil resistance; the number and configuration of coils where the configuration of coils can vary in location in the atomizer (such as the top or bottom coils), which can affect the wicking rate of the coil; and the configuration can also vary in design (such as a standard coil versus a Clapton coil), which can affect the surface area of the coil. The coil parameters also include the coil gauge, which is the size of the coil; and coil failure testing, which is the number of use cycles until the coil fails (which may include abnormal buildup, irreversible change of resistance, and an unpleasant taste).

For the battery, the parameters include the milliamp hour rating, which is the storage capacity of a specific battery, which delivers a certain level of milliamps for 1 hour; and the

voltage and current operating ranges, which is the range of minimum to maximum voltage and current output respectively during normal use.

For the power distribution unit, the parameters include the voltage, current, and wattage operating ranges, which is the range of minimum to maximum voltage, current, and power output respectively that a power unit can achieve during normal use; the wattage deviation, which is how much the actual wattage delivered to the coil deviates from the wattage displayed on the user interface; the temperature cutoff, which is the highest temperature the manufacturer claims the atomizer coil will not exceed; and the temperature control deviation, which is how much the actual temperature of the coil deviates from the temperature displayed on that user interface.

As the guidance and product evolves, there may be other parameters to discuss.

The engineering analysis of the second part of 910(b)(1)(B) focuses on the basic principles of product operation, which primarily encompasses the heating source and operation.

The purpose of the product operation is how the product is supposed to be operated. As stated in the draft guidance for

PMTAs on ENDS, the full description includes the time to consume a single unit; how the consumer will ignite the product and by what means; if and how the consumer can adjust the performance, change the product characteristics, or add or subtract ingredients; and other types of products that can be used together.

The engineering analysis of 910(b)(1)(C) focuses on the basic principles of product manufacturing, including the process and controls.

The purpose of the manufacturing process is to evaluate whether the product conforms with the product specifications. As stated in the draft guidance for PMTAs on ENDS, the manufacturing process information encompasses the manufacturing, packaging, and control site facilities; the manufacturing and production activities, which include the detailed steps of each module of the manufacturing process in order to provide enough information on manufacturing steps so that the process as a whole is understood and how the product is made could be visualized. It would also be helpful to have the managerial oversight and employee training and activities related to identifying and monitoring supplies and the product supplied.

The purpose of the manufacturing controls is to ensure product-to-product consistency. As stated in the draft guidance for PMTAs on ENDS, the controls description includes the product design controls encompassing the health hazard analysis, which is the correlation of the product design attribute with public health risk and mitigations for identified hazards. It also includes human factors, which will be later discussed by Captain Cheng.

The control descriptions also include the validation and verification activities in order to ensure product and methods are meeting the standards; the release testing procedures to prove the final product meets the specifications; and any corrective methods used to fix any products or deviations that do not meet the intended characteristics.

An example of the product manufacturing can be found in the Swedish Match North America PMTA. The engineering analysis included the manufacturing, packaging, and control site facilities; the manufacturing steps; and the quality control and performance criteria.

In conclusion, the product engineering generally includes the product design, which encompasses the target specification, range limits, and test data; the principles of operation, which

includes the heating source, product use, and product adjustment; and the manufacturing, which includes the production steps, supplier information, quality controls, and release testing.

Thank you.

(Applause.)

DR. DRESLER: Our next presenter is Dr. Steven Yee, who will be presenting on Toxicology Topics on Premarket Tobacco Product Applications.

Steve.

DR. YEE: Good morning. As mentioned, my name is Steven Yee. I'm a toxicologist in the Division of Nonclinical Science in the Office of Science. The title of my presentation is Toxicology Topics on Premarket Tobacco Product Applications. My talk is going to differ slightly from others in this seminar since I'm going to be talking about a number of topics in a very broad manner.

What I'd like to do first is to present a background on ENDS, electronic nicotine delivery systems. This will help orient us as we move forward in this discussion. From there, I will present a little bit of a primer on what toxicology is. This will help us gain a better understanding as we talk about

how toxicology applies to PMTA.

Now, two points I need to make right at the onset is, first, these slides will be available through the webcast. There's a lot of information here, some of which I may not talk about in its complete entirety. But you will have a chance to look at those slides later on; you can peruse it at your own pleasure. The second thing I want to say is that there are a number of web links, web source resources available that are quoted in the slides, and these are certainly available during the break.

Now, before I begin, there's a couple of remarks I need to make. And the first is that the FDA is required to evaluate the risk and benefits to the population as a whole, including to tobacco users and nonusers. The FDA does not currently require specific studies be conducted for the toxicology portion of product applications.

This presentation provides some examples of the types of studies that may inform an understanding of the toxicology of the tobacco product. This is not meant to imply that all these types of studies are necessary to support a product application.

So to reiterate what I'm going to do in my presentation is

present a very brief overview of ENDS products; talk about what toxicology is, why it's important; and then talk about how toxicology is applied to a PMTA.

So let's focus your attention first on this little figure here. This certainly shows a range of possible ENDS products. There is no standard definition for ENDS products, and there is certainly a variety of designs as well as ingredients. What we can say is that there are two major components, two ENDS products: that is, the cartridge or refillable tank of solution which contains what's known as e-liquid or e-juice, which contains, of course, nicotine, flavorings, as well as other ingredients; the other part of it is there's an electronics portion that contains a battery-powered heating element or atomizer as well as a controller. This presentation will focus on e-cigarettes as well as cigalikes.

So this is actually an example of an ENDS product. In 2014, Zhu et al., a recent study, that approximated greater than 450 different brands of ENDS products. Certainly the numbers have changed by now. E-liquids themselves are heated via an atomizer into an aerosol, which is also known as a vapor. As we mentioned, e-liquid contains a number of products, including humectants and solvents (for example,

propylene glycol and vegetable glycerin, which you're all familiar with), nicotine, as well as flavorings.

In that same study by Zhu et al., the study estimated there were over 7,700 different unique flavors; that has certainly changed by now. Aerosol itself provides nicotine, provides the flavor as well as a physical sensation similar to that of inhaled tobacco smoke.

So let's focus your attention on this graph here, this figure here of a human. This actually shows the route of inhalation for e-cigarette aerosols. Some small part of it, of nicotine may be absorbed in the mouth, but the route of exposure for e-cigarette aerosol is the inhalational route. Now, let me make a scientific distinction here. Although we refer to aerosols as vapors, there's actually a very distinct difference. E-cigarettes really, it's just not a mixture of simple steam and water. It's actually a mixture of both aerosols and vapors.

So, by definition, a vapor is a gas formed by boiling or evaporating a liquid. Aerosol is a suspension of tiny particles, solids or liquids or both, as contained within a gas. So, in essence, e-cigarette aerosols, these really consist of liquid ultrafine particles or solids in condensed

vapor.

Now, for the remainder of my talk, we're going to pretty much say that e-cigarette aerosol is not only the particle phase but contains that vapor phase. At the end of my talk, I'm going to make a little distinction to help us along in understanding some studies that will be helpful.

So focus now on this next slide. And this shows a figure of the lung as actually its smallest component, the pulmonary alveoli, where gas exchange is going to occur, where oxygen is going to enter the bloodstream. This is the site where the aerosol itself, which contains harmful chemicals such as TSNAs and carbonyls as well as ultrafine particles, is going to enter the bloodstream, many of which are toxic and carcinogenetic. The ultrafine particles themselves are comparable in size and number to particles of cigarette smoke.

Now we're going to talk about TSNAs and carbonyls a little later on, but I should say TSNAs are part of the particles within the aerosol and carbonyls, which are formaldehyde, acetaldehyde are part of the vapors.

Okay. So now I'm giving you a grand tour of what I previously presented. All right.

So we already alluded that the potential source of

toxicants are from liquid: the flavors and additives, the individual components' chemicals; impurities; degradation of products. But there are also other sources of toxicants; this includes the device itself. Toxicants may be increased or introduced from a misuse of the product design, also from the contaminants or also leachable materials from the tubing or from the heating element or the container itself. So there are other sources of toxicants that are apparent, not just from the e-liquid itself.

So we can certainly say that from a commonsense point of view, that breathing in anything other than air will have adverse health effects. Smoking and e-cigarettes do have health effects. Depending on the product design of the e-cigarette itself and smoking behavior, there are reduced toxic compounds compared to that of combusted cigarette, but there are still health effects.

Now, will health effects in the form of carcinogenicity or lung and heart, liver disease be similar to that as occur in combustible cigarettes? Well, that is not yet fully understood. Where I'll be speaking, in short-term effects, we know that there are respiratory issues. Increased heart rate and blood pressure, nausea, and coughing are observed.

Again, long-term health effects such as cancer risk, the effects from lung and cardiovascular systems are to be determined. Moving forward, greater understanding of the health effects as well as consumer research will add to the scientific base. Now, despite not fully understanding what the long-term health effects are, we certainly can understand, to get a sense of what would be informative to make a decision based off the toxicology profile of e-cigarettes, toxicology profile in the sense of characterizing the toxicologic as well as assessing the health effects of the e-cigarette.

So before we move on in our discussion of talking about potential e-cigarette toxicants, I think a primer in toxicology is necessary. And this will help us understand what toxicology is, and it's important for determining the potential health effects from e-cigarettes.

So as I said, toxicology basically focuses on how deleterious health effects can arise from exposure to chemicals in e-cigarette aerosol. Now, from the draft guidance on PMTA for ENDS, which is available for comment, we know that FDA will assess the toxicology of the product to determine whether the health effects of using the product would have a detrimental effect to users' and nonusers' health.

So let's look at what an exact definition of toxicology is. Well, toxicology is the study of adverse effects of chemicals on living organisms. The basic principle of toxicology, often called the maxim of toxicology, was developed in the 16th century by Paracelsus, and the maxim translates to "The dose makes the poison." Now, what that means is that most non-carcinogenic chemicals will be harmless in small amounts but harmful at larger amounts. The exception to this is carcinogens. In most cases, any increase in carcinogens, the exposure to carcinogens, will result in increased risk of toxicity, in this case cancer. By definition, dose is the amount of a chemical that comes into contact with a living organism. Dose is affected by the route of exposure.

Now, the common noninvasive routes of exposure are, in other words, ingestion; dermal, your skin; and inhalation. So important point here is that for a given dose, for toxicity to occur, there is going to be different -- the different routes of exposure will lead to different toxicity.

Toxicity is the degree to which a chemical is harmful to a whole organism or in part. Now, some examples of toxicity, as listed here, include respiratory toxicity, the adverse effects of pulmonary tissue, on the nose, the trachea, and the lungs;

as well as carcinogenicity, cancer in humans or animals. Now, for carcinogenicity, there's no threshold dose. Any exposure has some risk. Now, some other forms of toxicity which will actually come up in this presentation include cytotoxicity, which means adverse effects to the cells; cardiovascular toxicity, affecting the heart. Another term that will come up is genotoxicity, and genotoxicity is damage to DNA within cells that will lead to mutation and then on to cancer. The dose-response relationship of a chemical helps to assess its toxicity.

Now, one term that often comes up, as developed by the dose response, is what's called an LD50, the lethal dose in 50% of animals tested; this is a measure of acute toxicity. The lower the LD50 of a chemical, the more toxic that chemical is. Other terms, important terms in dose-response relationship that comes up is what's called NOAEL, a dose at which there is no observed adverse effect, and LOAEL, which is lowest dose at which an adverse effect is observed.

Estimation of human risk from animal studies is possible using standardized toxicological methods. For example, this is risk assessment: determination of the probability that an adverse effect will result from a defined exposure. Now, many

relevant toxicity studies defining adverse effects in animals can be found in the published scientific literature. Now, risk assessment is a very complicated field, certainly more complicated than -- talking more detail here. But there is an upcoming workshop on risk assessment taking place next month. I think it will be here actually, at the Marriott. And for more information, you can consult this web link. Again, that will be available during the break.

So now that we've touched upon toxicology, let's talk about how toxicology affects PMTA. First, actually, let's first talk about e-cigarettes in general. Now, certainly e-cigarettes contain nicotine, which is the primary addictive substance, but the aerosols themselves contain a variety of respiratory toxicants and carcinogens.

Some examples of these include propylene glycol and glycerin, which are respiratory toxicants (they are, again, humectants, solvents) that we talked about earlier; tobacco-specific nitrosamines (these are carcinogenic, they are formed from nicotine); as well as carbonyls, which we alluded to earlier (formaldehyde, a carcinogen, as well as acetaldehyde and acrolein), and these are carcinogens or respiratory toxicants. Carbonyls are formed actually from the

decomposition of propylene glycol and glycerin when it comes in contact with the heating element.

Now, flavorings themselves can be cytotoxic. Certainly, I think Dr. Cheng talked briefly about diacetyl, that's a popcorn flavoring, and cinnamaldehyde is also. It's been shown to be cytotoxic in vitro to -- these are cell lines actually, pulmonary cell lines. And the long-term effects of these flavorings is unknown at this time.

One thing that often comes up is flavorings and additives are referred to as GRAS; it's generally recognized as safe. GRAS, however, applies only to ingested food. Now, tobacco is not food, and the e-cigarette is going through an inhalational route. Again, this refers back to the fact that toxicity is going to be different by the route of exposure. This is important.

Now, one thing that Caliope talked about was the Tobacco Product Master Files. The nicotine and flavor suppliers or e-liquid suppliers should have a lot of -- should have this relevant toxicity data, and that certainly can be provided to the e-cigarette manufacturers.

Now, from the draft guidance on PMTAs for ENDS, which is available for comment, to help inform us on the toxicology of

ingredients, with the exposure assessments of e-cigarette constituents -- this again to help inform the toxicology of the ingredients, exposure assessments of e-cigarette constituents -- also includes harmful, potentially harmful constituents that Dr. Cheng so eloquently described. And these HPHCs are used to evaluate health effects.

Examples of HPHCs, many of which we just talked about, include but are not limited to acetaldehyde, acrolein, benzo[a]pyrene, ethylene glycol, formaldehyde, glycerol, nicotine, propylene glycol, as well as TSNAs.

Assessment involves direct measurements as well as exposure estimates. It would be very informative via the same route of exposure. Other information that is informative includes exposure duration, inhalation rate, consumption rate, and body mass. What's also informative, if the information accounts for the range of exposures from a light user to -- that should actually be a non-intense user versus an intense user. And that will help evaluate the dose-response relationship.

To continue this vein, again, the dose-response assessments over a range of exposures are important, and higher exposures will help inform of any potential health effects.

Again, this is from the draft guidance.

For non-carcinogenic constituents, reports that define the threshold of toxicity, especially the NOAEL and LOAEL, are important. We just talked about what the NOAEL is, the no observed adverse effect level, and LOAEL, the lowest observed adverse effect level. For carcinogenic constituents, if only the high exposure studies are available, an assumption of linearity can be made for low-dose extrapolation.

For both carcinogenic and non-carcinogenic constituents, user and non-user exposure can be compared to available dose-response information.

From the draft guidance, which is again available for comment, there are a number of -- the following toxicology studies may be informative: These include analysis of constituents and other toxicants under both intense and non-intense use; again, this is the range of exposures. Toxicology data from the literature. In vitro toxicology studies, these are studies within cells or tissues. Examples of such studies are genotoxicity studies as well as cytotoxicity studies. We talked about genotoxicity and cytotoxicity. Other studies include in vivo toxicology studies in animals; this is to address unique toxicology issues that cannot be addressed by

alternative approaches. Other studies that can be used is computational modeling of toxicants in the product to estimate the toxicity of that product.

Again, from the draft guidance, example of information that may be helpful for toxicological evaluation include, but is not limited to: chemical constituent information and properties; toxicological evaluation of the ingredients and mixture of ingredients in e-liquid and aerosol produced; the toxicological endpoints of health effects (this includes cytotoxicity, genotoxicity, carcinogenicity, and respiratory toxicity); also, ingredient exposure kinetics, metabolism, and deposition and elimination profile. This is something we didn't actually discuss about, but it's something that Captain Lindsey mentioned about pharmacokinetics and pharmacodynamics.

Pharmacology is, actually, the opposite side of the coin of toxicology. Toxicology is the study of adverse effects on a living system, but pharmacology is the study of beneficial effects. But we're dealing here with toxicology. Toxicokinetics is essentially how the body handles a chemical, and toxicodynamics is what the chemical does in the body that moves forward into toxicity. So what's important here is understanding how the body deals with this chemical and

certainly the exposure kinetics. Certainly, the toxicokinetics is important. I think that's all I'm going to mention about that.

Now, other examples of information that may be helpful to toxicological evaluation include extractable, leachable information from the product; conclusions for toxicological concern from the ingredients in the aerosol and from the use of the product; as well as physiochemical information on mixtures of ingredients in the product due to parameter changes.

Now, one thing I want to say is that when you're looking back at using the literature itself, some studies are simply more informative than others. So within the published literature, generally speaking, good scientific studies are studies that are more informative than others, and they include but are not limited to well-designed studies that have proper controls; they are peer reviewed, publicly accessible, readable English or translated. Author affiliations are well known, or funding sources, as well as conflicts of interest. Use of grey literature is generally avoided. Now, grey literature is abstracts or scientific posters presentations. These do not provide the strongest scientific evidence since these are not peer reviewed.

Good scientific studies avoid partial quoting of original sources that omit qualifying information and do not rely upon the absence of evidence as the evidence of absence. Just because the paper doesn't say anything is not evidence that such-and-such does not occur.

Continuing along this vein, what studies are more informative, generally speaking, is studies that consider phase consideration, product design and ingredient testing, in vitro study design, in vivo study design, data interpretation and analysis, and user and nonuser exposure.

So let's briefly talk about these. In terms of phase considerations, now this is what I talked about earlier about aerosols and vapors being distinct. In study designs to test aerosols, it needs to consider both phases, aerosol phase as well as the vapor phase. Dilutions and preferential phases may obscure underlying component toxicity.

In terms of e-cigarette design and ingredient testing, e-cigarette design and settings should be well documented -- are well documented, excuse me. Ingredient testing is reflective of the actual ingredient levels in the test product, not some exaggerated amount or some miniscule amount.

In terms of in vitro study designs, studies that are more

informative would have these. They would follow set guidelines, follow good laboratory practices, have proper controls, and test relevant cell lines. In other words, if you are looking at lungs, you would be looking at lung cells.

Continuing on with in vivo study designs, for example, again follows set guidelines; it uses realistic and non-diluted exposure regimens; uses proper controls; they are well designed; understand study limits. For example, 90-day studies are not carcinogenicity studies. I'm having trouble with that word. Again, carcinogenicity studies are 2-year studies.

Data interpretation and analysis, for example, uses proper statistics. It is not underpowered, in other words, small number of replicates. It discusses all the biological and statistically significant endpoints, and it has complete analysis of results.

In terms of user exposure, it comes back to accounts for range of exposure from the non-intense to intense user. Non-user exposure, for example, characterize the impact, health effects of new tobacco products on the non-user health.

So as we move forward, generally speaking, we can say that publicly available e-cigarette toxicology data is increasing as we move forward with future studies hopefully. That will be

more informative. We will consider the use of standardized testing paradigms, for example, validated inhalation exposure systems, exposure generation and monitoring, exposure regimens, and biomarkers of exposure. Also what would be more informative is studies that have sound study design, avoidance of inherent study issues that we just talked about, including low sample numbers and inadequate controls.

Now, here is a list of what resources -- if you desire to learn more about toxicology, again this is available during the break.

And here is to understand more about the scientific studies involved. Certainly, you can contact a toxicologist who can help you along in the toxicology part of the PMTA. Certainly, if you want to look at the scientific studies themselves, there's a number of resources you can search: Google, Google Scholar is always good, PubMed, TOXNET.

Okay. Well, that was nice. That's what PubMed looks like, and this is what I look like.

(Laughter.)

DR. YEE: Well, at least my hair is combed.

Well, there's supposed to be a summary slide in here. And to summarize, toxicology is the study of adverse effects of

chemicals on living systems. It helps elucidate potential health effects of chemicals from e-cigarette products, and basics include dose response, toxicity, routes of exposure, carcinogenicity, and risk assessment.

E-cigarette toxicology data is available for toxicants and carcinogens. Manufacturers of e-liquids, flavors, and other ingredients can provide toxicology data in a master file that should be available. And toxicology data may be available in the published literature to the extent the product under review is similar to that in the literature.

To help understand the toxicology of the ingredients, in understanding what the toxicology profile is, again toxicology profile is the characterization of the toxicologic as well as adverse health effects of that constituent and the dose-response assessment over a range of exposures. Informative literature-based reports include those that are well designed and peer reviewed.

Thank you, all right.

(Applause.)

DR. DRESLER: Okay, our last speaker for this session will be another toxicologist, Greg Gagliano, and he will be presenting on the Environmental Considerations for Premarket

Tobacco Product Applications Submitted to CTP.

MR. GAGLIANO: My name is Greg Gagliano. I'm a toxicologist in the Environmental Science Branch, Division of Nonclinical Science in the Office of Science, and today I'll be speaking to you about the Environmental Considerations for Premarket Tobacco Product Applications Submitted to CTP.

And specifically, I'll be going over:

- What is NEPA?
- NEPA purposes
- What FDA actions are subject to NEPA?
- CTP's NEPA process
- Some of the basic elements of an Environmental Assessment
- And some applicant resources.

So what is NEPA? NEPA is the National Environmental Policy Act that was signed into law on January 1, 1970, and that's a national policy that will encourage productive and enjoyable harmony between man and his environment.

And what's the purpose of NEPA? The three main purposes are to promote efforts which will prevent or eliminate damage to the environment and biosphere and stimulate the health and welfare of man; also, to enrich the understanding of the

ecological systems and natural resources important to the nation; and finally, to establish a Council on Environmental Quality. So that's the environmental law that requires environmental assessments.

And what are the FDA actions that are subject to NEPA? First, the promulgation of new regulations, and the other is the requests for private action. So an example of a private action is a marketing authorization for certain product applications such as tobacco products or a drug.

CTP's NEPA process is spelled out in 21 C.F.R. Part 25. Specifically, 25.15(a) states that all applications or petitions requesting agency action require the submission of an environmental assessment, or EA, or a claim of categorical exclusion, and that a claim of categorical exclusion shall include a statement of compliance with the categorical exclusion criteria and shall state that no extraordinary circumstances exist.

It also states that failure to submit an adequate EA for an application or petition requesting action by the agency of a type specified in 25.20, unless the agency can determine that the action qualifies for exclusion, is sufficient grounds for FDA to refuse to file or approve the application or petition.

So simply stated, if your application does not have an environmental assessment, it may be rejected by the agency.

So what are the basic elements of an EA? Well, 21 C.F.R. 25.40(a) sets forth some of the basic elements, and these are: a brief discussion of the need of the proposal; the alternatives as required by Section 102(2)(E) of NEPA; environmental impacts of the proposed action; environmental impacts of any alternatives that are identified; environmental issues relating to the use of the tobacco product; environmental issues related to the disposal from the use of the tobacco product; and a listing of the agencies and persons consulted.

So a brief discussion of the need for proposal: That means what is the applicant seeking? In this case, the applicant is seeking a premarketing authorization so that a new tobacco product may be introduced into interstate commerce. And what are the alternatives that are required by NEPA? Well, mainly it's the no-action alternative, although others may exist.

The environmental impacts of the proposed action alternatives include the impacts if the product is authorized and subsequently marketed, and impacts of the alternatives, in

our case, no action. And we also need to remember that we have to identify the product for which we're identifying the impacts and keep the EA specific to that product.

Environmental issues relating to the use and disposal from the use of the tobacco product: So again, what is the product that we're talking about and what -- we need to discuss the disposal of packaging for that product. Another requirement is the list of agencies and persons consulted. So if you consult CTP for advice or information, that should be listed under this section within the EA. If nobody was consulted, no agency or persons in the agency were consulted, then a statement that simply says that no agencies or persons were consulted should be included.

And some applicant resources: Again, the Center for Tobacco Products, AskCTP e-mail or the phone, you can call in. If you've already submitted an application, you can contact your Regulatory Health Project Manager. We also have some examples of EAs that are posted on the CTP website, and I highly recommend that you look those over because that will give you an idea of these basic elements that I just discussed, what they look like and the current philosophy of the Agency.

Also, there's a very nice compliance webinar on the

Compliance Webinar webpage that goes into a bit more regulatory detail than I have today. It's about a 20-minute webinar; it's not very long, and that will provide you some additional details. And probably most importantly is that if you do have any questions, need additional information prior to submitting your application, please e-mail the AskCTP e-mail address or call in for the information.

Thank you.

(Applause.)

DR. DRESLER: Okay. So I'll have the presenters come up to the front. Be thinking of your questions, and raise your hand and get one of those white cards, or if you're online, please submit them in.

(Pause.)

DR. DRESLER: Okay. And again, I have some questions that came in beforehand, so let me start out with one of those as we're getting the other questions coming in.

Do we test only e-liquids or test both e-liquids and the aerosols? Who wants to take that question? Do we test only e-liquids, or do we test both the e-liquids and the aerosols?

DR. CHENG: I think that's for me.

As we have discussed in our slides, e-liquid test may

provide information, for example, the formulation verifications, the information of both ingredients and unintended ingredients, and also the reaction products. And the testing for the aerosols may provide information as discussed in our slides, the constituent information. So you're welcome to consider the appropriateness of these testing to your products and make decisions.

DR. DRESLER: Okay. Which HPHCs should be tested for?

DR. CHENG: Our draft guidance on PMTAs for ENDS, which is available for comment now, we had a slide in our chemistry presentation, and it has a list that's proposed by the draft guidance for your consideration.

DR. DRESLER: Greg, this will be for you.

Can you please explain in detail the environmental assessment and the length of time they encompass? How much time does it take to complete an environmental assessment?

MR. GAGLIANO: Okay, for the first part, I think the basic elements that I presented here give adequate guidance on what needs to be included. Certainly, go into the website, looking at our example EAs that are public documents and looking at that webinar that goes into a little bit more regulatory detail, and finally, if you still have questions, certainly go

to the AskCTP e-mail and send us a question. As far as the amount of time that it takes, it's really a variable process, so we really can't comment on how long it takes to complete an EA.

DR. DRESLER: Okay. So for toxicologic and environmental impact expectations, what is the reference standard and expectation for toxicological work within this category? What is the scope and expectation for environmental impact analysis? Is there an available reference standard?

MR. GAGLIANO: There's no reference standard available at this time, and again, you can consult 21 C.F.R. Part 25 for additional specific details about environmental assessments, and again, reference my presentation as well as the references that we have available on our website.

DR. DRESLER: Will animal inhalation studies be required?

DR. YEE: I think the draft guidance addressed that. They can be informative.

What?

(Off microphone comment.)

DR. YEE: Yeah, but -- yeah, right. Exactly. Nothing is required. It helps.

DR. DRESLER: Is CTP expecting carcinogenicity studies

results with each PMTA?

DR. YEE: They're not necessarily required, but they can be informative.

DR. DRESLER: Does the environmental assessment have to follow a specific format?

MR. GAGLIANO: At this time, there's no specific format, but again, I would recommend looking at the format that was used for other tobacco products, and that's available on our website.

DR. DRESLER: Okay, I'm going to -- so my next questions are longer, and then this one I'm going to attempt to answer, okay.

So manufacturers who have already submitted information on an independent standard for manufacturing through organizations such as AEMSA, which is the American E-liquid Manufacturing Standards Association, will companies be able to refer FDA to these organizations in the PMTA as AEMSA maintains detailed lists of our ingredients, lab conditions, etc.?

So FDA can reference documents submitted in the PMTA and Tobacco Product Master File with those letters of authorization as discussed in Session 1. You should plan to submit manufacturer information about your product and any references

you choose to follow in your PMTA.

So now this is a longer one, okay. So with respect to engineering considerations, you indicated that PMTAs products procedures should be compared to other currently marketed products in the same category. Given that the properties of other products is often proprietary data, how specific do you expect this comparison to be, or would it be limited to publicly available data, i.e., in the packaging, what's in the packaging? So the question is, given the properties of -- comparing the properties of other products that is often proprietary, how specific do you expect these comparisons to be?

MS. SINGH: So it doesn't -- okay. It doesn't have to be specific. It just needs to give us enough information to be able to make a comparison, and I think I'll let -- Dr. Chang might be able to answer that later in her discussion when she talks about the comparators.

DR. DRESLER: Okay. Regarding toxicological considerations, you suggest that the applicant account for a range of exposures, including light and heavy use. Does CTP have specific suggestions regarding how to evaluate the range of exposures?

DR. YEE: I don't think we have specific guidelines at this time.

DR. DRESLER: Okay.

DR. YEE: Yeah, we really don't have guidelines at this time, but we're certainly looking into it.

DR. DRESLER: Okay, Dr. Yee, this is for you also. You mentioned modeling. Is there an accepted software for computational modeling for toxicants?

DR. YEE: As far as I know, there is no specific acceptable software, but you can certainly use a variety of software.

DR. DRESLER: Okay. And how is --

DR. YEE: That, actually, I'm not really too certain of. That may be a risk assessment question that someone else could address.

DR. DRESLER: Okay. Or when I hear you say something like that, I'm also thinking that we have that upcoming --

DR. YEE: Oh, yes.

DR. DRESLER: -- workshop on risk assessment, too, which might be a very good source for this.

DR. YEE: Right, right.

DR. DRESLER: Okay. I'm not sure I'm going to be able to

say this word, Steve. How is accumulative -- I think accumulation of toxicology handled? So I'm thinking what this means is that as people use it more and more, so perhaps chronic use?

DR. YEE: Right, I think --

DR. DRESLER: Accumulative --

DR. YEE: Yeah, certainly from a daily exposure rate or something like that.

DR. DRESLER: Um-hum.

DR. YEE: Certainly, information on that would be very informative.

DR. DRESLER: Okay. And the question is how is it handled? How is accumulative toxicology handled? So --

DR. YEE: Well, certainly as you're looking at the characteristics of it, that can help to inform a decision as to how much has accumulated per day and whether or not there will be toxicity involved. I think that's what the question is asking.

DR. DRESLER: Okay. And you're saying it would be assessed as part of the review?

DR. YEE: Yeah, it will be part of the review, yes. It would help to be informative, certainly.

DR. DRESLER: Okay. Are forced degradation studies expected as a prerequisite to shelf life or stability studies? So are forced degradation studies expected as a prerequisite to shelf life/stability studies?

DR. CHENG: Could you repeat the first part, please?

DR. DRESLER: Sure. So forced degradation studies, are they expected as a prerequisite? So if you're looking at shelf life and stability studies, does the applicant have to do forced degradation studies?

DR. CHENG: I think that may be adopted from the drug side, that term. But as far as I know, I am not familiar with this term in the tobacco field. But again, if it is relevant, and you think it's necessary to demonstrate the stability of your product, you're welcome to consider it and provide justification explanation for why this information is used for, for example, bridging information, etc.

Thank you.

DR. DRESLER: And I think that your answer probably will go along with the follow-up to this.

If so, would this requirement extend to every flavor at every nicotine strength? So an applicant is going to have multiple flavors, multiple nicotine strengths. Do they need to

have those forced degradation studies?

DR. CHENG: I think Caliope, in Caliope's response to one of the questions, it says that although you can package in all the information for all the products into one submission, we tend to process them as each individual product, and each one you need to have clarifying information for each product, and for the flavors and the ingredients, it is the same thing. And if you have the information for each flavor and each ingredient, please provide the information and specify which product has this information.

DR. DRESLER: Okay. So a hypothetical situation. A supplier goes out of business, must source functionality -- identical component from other supplier. You discover a safety issue, and you must notify -- must modify the design. How does the Agency suggest that these modifications be documented for inclusion in the August 8th, 2018 PMTA?

So this is a hypothetical situation. A supplier goes out of business, and the applicant must source functionally identical component from another supplier, but they discover a safety issue and they must modify the design. How does the Agency suggest these modifications are documented?

(Off microphone comment.)

DR. DRESLER: A policy question? Okay, thank you. All right, so policy question, so that's one that gets submitted into AskCTP.

(Off microphone comment.)

DR. DRESLER: Hypothetical, right. So AskCTP for that question. We need to have the real one come in. Thank you.

Oh, okay. Thank you. Oh, so what that clarification was is I couldn't read somebody's handwriting, and so please make sure it's legible.

Okay, does FDA expect that most ENDS manufacturers will need to commission animal toxicology studies and include such data in a PMTA or not need to commission? So this goes back to a question that I think we asked before. Is there a requirement to do animal toxicity studies or are they not required?

DR. YEE: I think I can address that again. Certainly, the animal studies are not required, but they are -- they can be very informative in helping us to make a decision. There are published literature out there which has done some animal studies already, and they certainly can be bridged to the information that you want to provide.

DR. DRESLER: Okay. Steve, this is staying with you.

You've given a wonderful overview of non-binding draft status guidance. Can you please elaborate on statutory requirements for toxicology reporting? Please point us to your statutory requirement for toxicological review.

DR. YEE: Well, FDA -- yeah, right.

(Off microphone comment.)

DR. YEE: We -- yeah. Certainly, we have to understand the health impact, but I don't think there is any standard reporting, as far as I know.

UNIDENTIFIED SPEAKER: There is a requirement for toxicological data, but we have to understand the health impact of --

DR. DRESLER: Okay, so let me repeat that, okay? So -- and I think it's something -- that's why I was kind of emphasizing you said it before, there is no requirement for toxicological studies, but the most important part is that the application make it very clear what is the protection for public health, and so however you are doing that, bridging studies or peer reviewed, etc., is that you need to make sure that the information is there in the applicant for the protection of public health.

Any more questions? Maybe we might have one pending, is

that what I'm seeing back there? We might have one that's being worked on? No?

Okay, going once, twice. You just -- oh, we do have one coming in online. So let me get that question as they come up, and then I will just say -- so it's 5 to 12:00. We were going to break at 12:30, so we're early, so this is telling you that we have more time for questions if you have more questions, to submit those in.

But we'll go ahead, and we'll take an hour for lunch, but that means we'll still come back early, and that means we would come back at 1 o'clock, so that gives you an hour and 5 minutes for lunch, which means we may finish earlier, but keep the questions coming in.

Caryn, is that all the questions? That is all of the questions, all right. Thank you very much, panel, for those good presentations and the questions, and we'll see everyone back at 1 o'clock.

(Whereupon, at 11:53 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

DR. DRESLER: Let's go ahead and get started. It still is a few minutes afterwards, and it is being recorded, so if anybody missed these opening, riveting words, they can get it on the webinar also. But let's try and stick somewhat to the schedule.

So welcome back. A couple of notices. It's not as packed now as it was earlier, but still, please be careful as we start getting more people coming in from lunch. I was asked to remind, no seat saving so we can fit everybody in here as possible.

The next thing is, is that the agenda that you have, can you please bring it tomorrow also so we're not printing out another set of agendas? So if you can bring that back tomorrow.

And then, also, there was a question that had come in after we had gone for the break, and we just wanted to make sure that we addressed this topic as well. So we're going to ask Dr. Kimberly Benson, who is the Director for the Nonclinical Division, to come up and address this question: Can you address again regarding the need for animal studies?

Dr. Benson.

DR. BENSON: I know this is a topic that everybody has a lot of questions about, so we want to make real sure that we're really clear. There are no requirements. You know, I came to CTP from the CDER world where there were regulations that said these are all the toxicology studies you have to do before you can submit an application. We don't have that.

What we have is the statute that says the product has to be appropriate for the protection of public health. So it's incumbent on the applicant to make that argument. The product has toxic ingredients in it, so the toxicology should be addressed. How you address that is on you because we do not have any regulations. So is it required that you do animal studies? No. Are we even recommending you do animal studies? No.

Are we recommending you do carcinogenicity studies? I reviewed many a carcinogenicity study in CDER. I appreciate what kind of a task that is for a product with a single active moiety, and here we're talking a complex ingredient. What I would say is if your product contains carcinogens, you need to address the potential carcinogenicity. I'm not saying that you need to do carcinogenicity studies with your product.

So hopefully, that clarifies it a little more, that we're not requiring or recommending animal studies. What we are saying is it's incumbent on you to make the argument that your product is appropriate for the protection of public health, and toxicology data as well as clinical data, that's the information that can address the toxic and the health effects of the product.

DR. DRESLER: Thank you.

Now we'll move on to Session 3, which is about Data Sources. And our first presenter is Catherine Corey, and she'll be speaking on National Estimates of E-Cigarette Use: Review of Publicly Available Literature.

Cate.

MS. COREY: Hello, my name is Catherine Corey, and I'm an epidemiologist in the Office of Science at CTP. My presentation will focus on National Estimates of E-Cigarette Use: Review of Publicly Available Data Sources.

National e-cigarette data may be one source among many an applicant can use to supplement or complement other behavioral information that may be submitted in a PMTA. This presentation begins by discussing sources of data on e-cigarette use from national youth and adult surveys as well as the PATH Study,

then provides published national estimates of e-cigarette use, subsequently reviews in broad terms how to access national e-cigarette data, and finally discusses some strengths and limitations of using national e-cigarette estimates.

We'll begin by discussing sources of national estimates of e-cigarette use. Before discussing e-cigarette measures specifically, I'll provide a brief overview of national surveys of health and tobacco use more generally.

National estimates of tobacco use in the U.S. population have been reported as part of federal health and tobacco surveillance for decades in the case of cigarettes. As the tobacco product landscape evolved, many federal surveys added new questions related to the use of e-cigarettes, smokeless tobacco, cigars, and hookah or waterpipe. At a minimum, national surveys usually include basic questions about ever or lifetime use as well as current use of tobacco products. These surveys can be used for a variety of purposes, including to estimate, at a point in time in the U.S. overall as well as across different subpopulations, the percentage or number of individuals currently using a tobacco product, formerly using a tobacco product in the context of adult users, or never using a tobacco product.

Now that I've provided a brief overview of national surveys of health and tobacco use generally, I'll discuss some issues related to e-cigarette use specifically.

The diversity of e-cigarette products on the market -- such as cigalikes, e-vaporizers, tanks and mods -- present certain considerations for measuring these products on surveys. One of those considerations is understanding the language consumers use to discuss and distinguish e-cigarettes. Researchers who study e-cigarette users have reported on these challenges, and I've noted on this slide here a few recent papers that have explored the terminology consumers use for these products.

Evidence from qualitative studies of adults suggests that the term "e-cigarettes" is generally understood to apply to the wide array of products. However, to reflect the range of e-cigarettes on the market and the varied ways users refer to them, some survey questions include clarifying information such as synonyms for the term "e-cigarette," like "vape pen" or "e-vaporizer," as well as common brand examples such as blu, Vuse, and the others listed here.

And in terms of federal sponsors of tobacco surveys, there is coordination ongoing to align e-cigarette survey questions.

A few additional things to note about e-cigarette measures on national surveys. At a minimum, national surveys usually include questions about ever e-cigarette use (in other words, use of one or more times in one's lifetime) as well as current e-cigarette use, which is typically defined as either now using e-cigarettes every day or some days or used on one or more of the past 30 days.

The survey data can be used for a variety of purposes, including to estimate, at a point in time, the percentage or number of individuals who currently use, have formerly used in the context of adult users, or have never used e-cigarettes. And later in this presentation I'll provide some examples of the prevalence of youth and adult e-cigarette use.

Finally, I'll note that in general, national surveys don't ask detailed questions on e-cigarettes related to such topics as the product attributes, including the device type or brands used; e-liquid characteristics, including flavors or nicotine concentrations; or use history, such as the number of times someone has used a product in their lifetime, or the frequency of use, such as the number of days, times used in a particular day.

For the purposes of this presentation, I want to explain

that because we're focusing on national survey estimates, the term "e-cigarettes" will often be used to refer to the array of ENDS products as described in the draft guidance on PMTAs for ENDS that's available for public comment.

So we're now going to move into summarizing national youth surveys that capture e-cigarette use, beginning with the National Youth Tobacco Survey. NYTS is a nationally representative cross-sectional survey of middle and high school students, focusing exclusively on tobacco use and its correlates. It is administered by the Office of Smoking and Health at the Centers for Disease Control and Prevention, with support from CTP. The survey is conducted via paper and pencil and is administered annually to approximately 20,000 students in grades 6 through 12.

Since 2011, questions have been asked about e-cigarette ever use and past 30-day use. In 2014, an NYTS e-cigarette module or special subsection was created on the survey. New e-cigarette questions have been added over successive cycles. Questions on the survey have addressed such topics as the frequency of lifetime use and number of days used in the past 30 days, the age at first use of e-cigarettes, susceptibility to e-cigarette use, and other topics listed here.

In addition to the NYTS, there are a few other national youth surveys capturing e-cigarette use. Monitoring the Future is conducted by the University of Michigan through a grant from the National Institutes of Health. It is an annual, cross-sectional, school-based, paper-and-pencil questionnaire administered to 8th, 10th, and 12th graders. There is also a longitudinal component that follows a subset of 12th grade participants. The survey captures information on behaviors, attitudes, and values regarding a range of substances, including tobacco. Beginning in 2014, Monitoring the Future added questions about e-cigarette use, attitudes and perceptions.

The Youth Risk Behavior Survey, or YRBS, is conducted by the Division of Adolescent and School Health at CDC. It's a biennial, cross-sectional, paper-and-pencil survey administered to high school students in grades 9 through 12. YRBS monitors a range of health-related risk behaviors, including tobacco product use. Beginning in 2015, YRBS added questions specifically on ever and past 30-day e-cigarette use.

Now we're going to move into reviewing national adult surveys that capture e-cigarette use, beginning with the National Health Interview Survey. NHIS is a nationally

representative health survey of the U.S. civilian non-institutionalized population, sponsored by the National Center for Health Statistics at CDC. NHIS is conducted via an in-person interview on a computer or tablet. Approximately 30,000 to 35,000 adults each year provide information on their tobacco status.

NHIS has been used to track U.S. adult cigarette smoking prevalence for decades, and over time, questions have been added on the use of other combustible products and smokeless tobacco. Starting in 2014, questions about adult e-cigarette use were added.

In addition to the NHIS, there are a few other national adult surveys that capture e-cigarette use. The National Adult Tobacco Survey is a nationally representative phone-based survey of U.S. adults, focusing exclusively on tobacco product use and its correlates. NATS was conducted last in 2013-2014, among approximately 60,000 adults ages 18 and over. E-cigarette questions on NATS include those related to ever and current use, all e-liquid flavors used, and switching completely from cigarettes to e-cigarettes.

The Tobacco Use Supplement to the Current Population Survey, or the TUS-CPS, is a U.S. adult survey administered in

conjunction with the Census Bureau's Current Population Survey. It provides tobacco-related estimates at the national, regional, and state levels. TUS was conducted last in 2014-2015, among approximately 240,000 adults ages 18 years and older. The 2014-2015 TUS includes e-cigarette questions on ever and current use, usual e-liquid flavors, switching from cigarettes to e-cigarettes, reasons for using e-cigarettes, and a few other topics.

Finally, the National Health Examination and Nutrition Survey, or NHANES, is a national health and nutrition study combining interviews, physical exams, and biospecimens. The 2015-2016 NHANES will be the first cycle to ask about use of e-cigarettes in the 5 days preceding the interview.

I'm now going to switch gears from talking about national cross-sectional surveys to describe the Population Assessment of Tobacco and Health, or PATH Study. The PATH Study is a nationally representative longitudinal study of tobacco use, its determinants and its health impacts, meaning that the PATH Study follows the same individuals over time, whereas the national surveys take a snapshot of the population at a point in time. PATH is funded by CTP and administered by the National Institute of Drug Abuse, part of the National

Institutes of Health.

The PATH Study measures include: tobacco product use and frequency, in order to understand changes in initiation, cessation, and relapse over time; attitudes, knowledge, and perceptions of e-cigarettes and other tobacco products; biomarker measures of adult tobacco product use; self-reported medical conditions and health status.

PATH is conducted via an in-home interview using audio computer-assisted self-interviews. The interview cycles began in 2013, and three cycles of data have been collected to date, with the fourth cycle scheduled to begin in the fall of 2016. Cycle 1 consisted of approximately 46,000 persons, ages 12 years and older, including 32,000 adults ages 18 and over and approximately 14,000 youth ages 12 to 17.

Some considerations when using the PATH Study data include that it has more comprehensive questions on tobacco use and frequency compared with national surveys. However, while PATH asks about the usual e-cigarette brand a participant uses, the study is not designed to analyze particular e-cigarette brands. However, brand-specific analyses can potentially be generated if sufficient number of users of a brand are included in the dataset. Finally, I'll note that in early waves of this study,

there is limited information on device type and e-liquid characteristics, including flavors and nicotine strength.

The Cycle 1 data are publicly available, and I'll share the URL for how to access more information about these data later in a slide. And I'll just note that the Cycle 2 data, the first year of follow-up data, should be available in the fall of next year.

Now that we've reviewed sources for national e-cigarette data, I'm going to present select national estimates of e-cigarette use. This slide presents trends and past 30-day tobacco product use among U.S. high school students from 2011 to 2015. These data were published in a Morbidity and Mortality Weekly Report, or MMWR, in April of 2016, and the details of the analysis can be found in that publication.

E-cigarette use, the red line in this graph, has risen rapidly among U.S. high school students from approximately 1.5% in 2011 to 16% in 2015, which corresponds to roughly 2.4 million high school students reporting use of e-cigarettes in the 30 days prior to the survey. The dashed vertical line in this graph denotes that the format of the question about past 30-day e-cigarette use was updated beginning in 2014. Also over this period from 2011 to 2015, the prevalence of hookah

increased, while the prevalence of cigarette smoking, cigar smoking, and smokeless tobacco use declined.

This next slide presents the prevalence of past 30-day e-cigarette use by sex and race/ethnicity among U.S. high school students in 2015. The colored bars represent the point prevalence, and the thin vertical black bars represent the 95% confidence intervals that correspond to those point estimates. E-cigarette use was higher among male students than female students, and e-cigarette use was reported to be lower among black students compared with students who are white, Hispanic, or other non-Hispanic race/ethnicities.

This figure illustrates the frequency of days a tobacco product was used during the past 30 days among high school tobacco users in 2014. These data were published in an MMWR in October 2015, and the details of the analysis can be found there. The red bars illustrate that the proportion of past 30-day tobacco users using on 1 or 2 days was generally similar for e-cigarettes, cigars, and cigarette users.

The report in which these data were published pointed out that it isn't necessarily unexpected that the use of tobacco products can be relatively less frequent in adolescents who are at the early stages of initiation and escalation of tobacco

use. The report also pointed out that even among those using one product on a few days, a high proportion are using at least one other tobacco product, increasing their exposure to nicotine and other harmful constituents contained in tobacco products.

Now I'll shift gears to adult estimates. And this slide presents current use of e-cigarettes according to demographic characteristics from the 2014 National Health Interview Survey. Whereas among youth, current e-cigarette use was estimated as use on one or more of the past 30 days, the NHIS and other adult surveys generally based current use on whether a respondent now uses e-cigarettes every day or some days.

These estimates were published in a National Center for Health Statistics data brief in October of 2015; 3.7% of U.S. adults reported, at the time of the interview, that they now use e-cigarettes every day or some days. Current e-cigarette use was about the same for men and women. Younger adults tended to be more likely than older adults to currently report e-cigarette use. And white non-Hispanic adults reported higher current e-cigarette use compared with adults who were Hispanic, non-Hispanic black, or Asian non-Hispanic.

This next slide presents the percentage of adults who

currently use e-cigarettes according to their cigarette smoking status from the 2014 NHIS. The left-hand chart in this slide shows that the use of e-cigarettes was highest among current and recent former cigarette smokers. Specifically, 15.9% of current cigarette smokers reported currently using e-cigarettes. Roughly 22% of recent former cigarette smokers, those who had quit cigarettes less than 1 year ago, reported current e-cigarette use. Approximately 2.3% of long-term former cigarette smokers, those who had quit cigarettes at least one or more years ago, have reported current e-cigarette use. And less than one-half of 1% of never cigarette smokers have reported currently using e-cigarettes.

Another way of looking at these data is presented on the right-hand side of this slide. The 3.7 percent of adults currently using e-cigarettes, that translates to roughly 9 million U.S. adults. Dual use of e-cigarettes and cigarette represented 6.3 million adults or roughly 2/3 of the 9 million who are current e-cigarette users. The remaining 1/3 of current e-cigarette users were comprised of former cigarette smokers or never smokers.

Now that we've reviewed national sources for e-cigarette data and presented some estimates of e-cigarette use, I'll

briefly go over how to access national data for e-cigarette use.

This slide provides the URLs for publicly available datasets that we've reviewed during this presentation. Those who are interested can go to these websites to find out more information about particular studies.

I wanted to emphasize that the types of estimates that I presented today are published in a variety of reports and publications that can be accessed by the public for free. That said, one may decide to do independent analyses of the public use files of national survey data.

The contents of public use files generally include the following: the data file itself in a variety of different formats, the associated variables, as well as the read-in instructions to open a dataset in a particular software program; the copy of the questionnaire or instrument itself; the methodology documentation which describes the design, sampling, weighting, and other processes; a codebook or data dictionary associated with the dataset as well as data tables that summarize key results. As I mentioned, the public use websites may also provide links to online reports and publications providing the types of summary estimates that I

have presented today.

Analyzing national tobacco public use data typically requires statistical software that can account for complex sample design, including the clustering, the stratification, weighting, and other procedures that are used to generate a nationally representative dataset.

And again, while published estimates from these surveys are publicly available, should one decide to do an independent analysis but lack the experience in using these types of data, there are firms with survey analysis expertise that can be contracted to conduct analyses.

I'm going to conclude this talk with some considerations for using national e-cigarette estimates. To summarize what's been covered in this presentation, I'll review some key strengths and limitations of national e-cigarette data.

National survey data can be analyzed for a variety of purposes, including to characterize current e-cigarette status at the population level, so who among the population are never, current, or former users of these products; to describe the burden of e-cigarette use across different subgroups, such as by demographic characteristics or current cigarette smoking status, as well as to monitor changes in use or related

behaviors over time.

The utility of national estimates may be limited since survey questions focus on e-cigarette use generally and thus lack information about such issues as brands used, the device type, or e-liquids used. Most survey data are cross-sectional, which precludes the ability to assess changes in tobacco product use within individuals over time.

In contrast, the PATH Study is longitudinal and therefore can assess changes in product use prospectively over time and also provides more detailed data about product use than most of the national surveys.

In conclusion, the e-cigarette market is dynamic, and product use has changed rapidly in recent years. National surveys can serve multiple purposes, including to characterize population-level e-cigarette use data broadly at a point in time and can provide contextual information in terms of overall trends of e-cigarettes as a class of products. However, national surveys may lack information about brand- or device-specific use and generally are not intended to understand individual trajectories of use over time. The PATH Study has comparatively richer product use information and follows youth and adults over time but isn't designed specifically to study

brand-level or device-level e-cigarette use. And finally, depending upon the product and the data source, an applicant may consider, for some products, bridging from the national data to the product under consideration when discussing population impacts.

Thank you. This concludes my presentation.

(Applause.)

DR. DRESLER: Our next presenter is Dr. Carol Christensen, and she will be speaking on Literature Review Methodology: An Overview.

DR. CHRISTENSEN: Thank you and good afternoon. Again, my name is Carol Christensen. I am an epidemiologist in the Office of Science, and today I'll be discussing with you the conduct of literature reviews.

So literature reviews are typically comprised of several steps, and today we'll be discussing the identification, evaluation, interpretation, and reporting of information from a body of studies that address a specific research question or a specific research topic.

So there are several reasons that literature review may inform a premarket tobacco application for an ENDS product, and the draft PMTA guidance for ENDS products discusses literature

search as a source of information that may inform an application. There's a growing body of literature on tobacco-related issues, and literature review methods provide a convenient way to bring together large amounts of information. Published literature may supplement product-specific studies and inform premarket tobacco applications, even though not product specific themselves.

This presentation provides a brief overview of the general literature review methods, and it's not meant to be a step-by-step instruction guide. There are, however, publicly available resources. There are books, classes, instructional videos available to learn a little bit more about this topic area, if unfamiliar. But please be clear that FDA does not endorse specific tools or approaches for the evaluation or interpretation of literature studies.

Generally speaking, reviewers of published literature describe each step of the review process, from study identification through individual study evaluation to how you bring together the overall body of literature, which includes consideration of the results in the context of the quality of the methods used to obtain those results. And in this way, the literature reviewer can promote openness and transparency as to

how conclusions from the literature review are formed.

Importantly, those who perform literature review will work at the beginning of the process to pre-specify the types of articles to select into the review and articulate factors to be used to evaluate individual studies as well as the overall body of evidence.

Best practices in this area include being as clear as possible about the decisions made throughout the process so that others can understand how conclusions are formed. Reviewers apply these methods consistently throughout the process to increase the credibility of the review.

It's human nature to select facts to support our own point of view. Of course, we're all guilty of that. However, pre-specifying methods by which literature articles are identified and evaluated ahead of time helps to avoid the cherry-picking of studies and again increases the credibility of the review.

The first step in the literature review process is identifying studies of relevance. Reviewers first consider the specific question or the issue or problem under study. For ENDS research, this may include scoping questions such as: Are all ENDS products to be included in the literature review or only specific subtypes of ENDS products? What health or

behavioral outcomes are of interest in this review? What types of studies are relevant, and what types of designs are most informative? Are studies in the human population needed to inform this question, or will experimental studies on laboratory animals going to suffice?

If unfamiliar with the topic area, there are several ways to enhance knowledge about available studies. Reviewers new to the topic area often seek a librarian at this stage, and review articles or summaries can provide background information quickly.

To seek information from the biomedical literature, publicly available databases can be used. Different library or scientific databases provide different types of information. These are some of the major biomedical databases in which ENDS literature may be found. And the hyperlinks are available on this slide.

PubMed includes a compilation of studies from the biomedical sciences, primarily performed and reported in the U.S., while EMBASE provides a similar constellation of literature studies and is inclusive of studies performed in Europe. Web of Science provides a wider variety of these types of studies and includes both U.S. and non-U.S. based studies.

Reviewers note that different library or public scientific databases may require different searching techniques or ways to input search terms.

Those performing literature review often write out the question or statement to narrow the focus of the review, so for example, in ENDS research, ENDS literature review. So a question could be what adverse health effects have been reported with e-cigarette use? Using the key words from the problem statement or issue statement can form the basis of a literature search string. For example, "adverse effects," "human health," "electronic cigarette" could be key words to populate a search string.

The process of defining relevant search terms is often iterative, and it can take several tries to fine-tune search terms. Reviewers often find working backwards from a key article can aid the development of a search string. So if you can find one great article that really fits well in your topic area, look to that article for what key words are listed and ensure that those key words are in your search string.

Those performing literature review begin searching biomedical databases only after defining the research question or topic area, identifying the relevant search terms and the

databases in which those search terms will be implemented, and the types of studies to be included or excluded. And upon clarifying these issues, then the reviewer begins the database search.

To ensure reviewers are communicating not only the results of the literature search but also the process by which the materials were identified, reviewers also note the dates that the search was performed and the databases that the literature search was performed.

Even the best search string is imperfect. Reviewers typically evaluate a larger set of studies than are ultimately included in the literature search. And at this stage, reviewers often apply the inclusion and exclusion criteria identified. It is common that reviewers will first scan the title and abstract of those sets of studies that come back from a literature search string and eliminate articles that do not meet the search criteria. And a second scan of results may include a full text review or the evaluation of the entire paper.

So upon selection of studies into the review, reviewers consider individual study methods and results, and this may include questions such as: Which of these studies is most

important to the topic area or to the question? Which are the most well executed, the quality of the methods? Which are the least well executed? Which are the most persuasive or informative to the question under study and supportive of the conclusions reached, and importantly, where are the gaps? If additional studies were to be conducted in this area, would the overall conclusion change? So these are some questions to consider when evaluating the literature.

As stated earlier, practices in this field include reviewing study results in the context of the quality of the study methods which produced those results. Those performing literature review may identify study quality criteria at the beginning of the literature review process, and these can include factors such as: The funding source or potential areas of conflict of interest among those who are performing the individual study. What is the study design, and how well is that particular design going to inform the question that you're looking into, and for ENDS research particularly, what was the method by which ENDS exposure or ENDS use was measured or evaluated? And what do you think, what's the quality of that methodology; other areas of strengths and limitations across studies can be identified.

If systematic review methods are utilized, reviewers may employ risk of bias tools to evaluate the degree to which literature studies may have been performed with systematic errors or biases. In performing study evaluation, the consideration of the potential for these errors or biases or mistakes and how the study was conducted is very important.

If there are multiple reviewers evaluating the literature, study quality assessment tools may be applied to studies in the review and assessed by multiple reviewers to ensure consistency.

In some scientific disciplines, there are numerous study quality tools available. In the field of epidemiology, for example, this review identified a total of 86 tools to evaluate study quality, comprising 41 simple checklists, 12 checklists with additional summary judgments, and 33 scales to assess study quality. While there are published and publicly available tools of this nature to bring together large bodies of information, again, FDA does not endorse any one particular tool or method.

To aid interpretation, literature reviewers may group studies within the entire literature review by level of study quality, in this example, low, medium, or high. While

subjective in nature, if identified at the beginning of the process, as in before you go to the literature and seek out those studies, and applied consistently by the reviewer or reviewers taking part in the literature effort, the evaluation of study quality using criteria can facilitate the interpretation of study results.

So, for example, literature reviewers may consider a low-quality study to have characteristics such as a very small sample size and only selected reporting of outcomes, whereas a medium-quality study may be considered to be those that are observational in nature, have a non-random allocation of participants to the exposure, and have a larger sample size. And a very high-quality study may be considered to be those that have a characteristic such as well-designed and randomized controlled studies or trials and a very good reporting of both positive and negative outcomes from those studies.

Considering study results in this way, reviewers may evaluate results in the context of the strength of the study methods that produced those results. And in this way, reviewers are less likely to be strongly influenced by significant study results from poorly designed and executed evaluations.

As stated, practices in this area include the consideration of the quantitative or qualitative results from literature studies in the context of the relative merits of the study design and methods. And in so doing, reviewers may address questions such as: Among the studies that were most well executed or well conducted, what were the study results? Do they support or refute the question or position identified? Would more studies in this area lead you to a different conclusion, and if so, what would those studies be, and what are those characteristics?

So when forming conclusions across a body of literature, reviewers may consider other factors such as study quality, the potential for error in the study design or methods, the relative sample size and the precision of the estimate, the overall magnitude and direction of the results and the consistency of those results, particularly among studies of similar quality. The relevance of the study to the research question, is it really on point? Is it in the population of interest, for example? And the adequacy of the overall set of studies to report the conclusion, are there major gaps or areas that the science really just hasn't gotten to yet? Those are all questions reviewers consider in reporting and summarizing

relevant studies from a literature review.

So when pulling together a literature review, the search methods and results should be considered, and it's incumbent for reviewers to report, again, the purpose of their review. This is kind of in a written summary of a literature review. What's the purpose reviewing the question or the topic under study, describing the methods used to gather up the studies and to inform the question? What factors or criteria were used to evaluate both individual studies and across studies of similar design, type, or quality? For some reviews that might be systematic in nature, risk of bias methods may be utilized and described as well. Literature reviewers also report the results of the studies included in the review, and how do those results inform the question, particularly again by studies of similar quality, and overall, what strengths or limitations of the methods, and how does that inform the results, in addition to an overall bibliography, of course.

So, in conclusion, it's important to note that FDA has provided some basic principles of literature reviews and not a comprehensive strategy. Specific expertise may be required, and reference librarians may be available to assist. FDA acknowledges that published literature may provide useful

information to help support a premarket tobacco application for an ENDS product. And when performing a literature review, including the identification, evaluation, interpretation, and reporting of studies regarding ENDS products, openness, transparency, and consistency are hallmarks to consider. There are publicly available resources to assist in understanding the methods and processes of literature review.

And on that point, these next several slides include some examples of how to develop a literature search strategy, if unfamiliar. And again, FDA does not endorse any one of these sources but provides them as examples.

Similarly, there are some resources to go to about literature review methods and particularly study quality review or risk of bias tools. And again, FDA does not endorse any one of these specific methods.

Similarly, how to write a literature review. These are web-based information sources that we make available for your information as examples.

And lastly, as noted in the presentation, a different literature -- sorry, different biomedical databases require search terms or search strings in slightly different formats. And these are some examples of search terms that may be useful

when looking at the three major biomedical databases.

Thank you for your attention.

(Applause.)

DR. DRESLER: Okay. So get your cards and your questions written, and raise your hand. And again, I have some questions that have come in online, so we'll start with some of those.

Okay. Cate, this will be for you. How should I use data from national surveys to support a PMTA application for my own product? Was that your whole presentation?

MS. COREY: I'll just start out by saying that FDA does not have any specific requirements or recommendations about how to use existing information or data in a particular PMTA. The information that I provided really is an overview of what national trends for both adults and youth look like.

One of the considerations for using national data is the fact that it is generally about the class of products, whereas an application may need to speak to the applicant's particular product itself. But if there are specific questions about your application and what data may be appropriate to support that, you can schedule a scientific meeting with FDA staff to review specific questions about the design or conduct of existing data or data that you may be interested in collecting yourself.

DR. DRESLER: Okay. This one will probably come for you also. Conducting a survey is expensive. If I conduct my own survey, how can I know if FDA will accept my results and give me marketing authorization?

(Laughter.)

MS. COREY: Right. So the design and conduct of surveys can really vary in scope and breadth, and it really is up to the applicant to decide (1) if they need to conduct a survey, which is a decision that they would need to make in the context of their own application; and then (2) if they do conduct a survey, what the breadth or extent of that work would be. And FDA can provide scientific insight around a specific question or survey design or data collection activity that an applicant might be interested in conducting.

DR. DRESLER: Okay. And this one is going to follow along that line. What does FDA require me to submit if I want to conduct my own survey and include the data as part of my PMTA? So very similar.

MS. COREY: FDA doesn't have any specific requirements about what elements need to be included as part of an application. If you go to the websites that were listed for some of these national surveys, that provides the types of

elements and information that might be important to include in your application.

DR. DRESLER: Okay. Can FDA provide templates for search strings, summary tables, or outlines of literature review to assist submitters?

Carol.

DR. CHRISTENSEN: Yeah, I'll take that one. For literature reviews, yes, there is no specific set of templates. What we provided were some broad guidance and principles about -- common in this area to perform literature reviews.

DR. DRESLER: Okay. And those are the questions that I have that came in before the meeting. I have another one working its way up that's coming from online.

Dr. Apelberg, the question, please. Thanks.

For Cate Corey. Can you please comment on the potential impact of prevalence estimates of the NYTS method change between 2011 and '13 and then from 2014 on?

MS. COREY: Um-hum, yeah. So when the e-cigarette use question was first added to the NYTS in 2011, e-cigarettes were part of a single question containing a series of products including snus, hookah, and other non-cigarette products. And applicants -- I'm sorry, participants to the survey would

acknowledge whether they had used that product in the past 30 days.

And as the prevalence of use increased, we realized that it was important to collect more detailed data on e-cigarette use among youth, and so we developed questions that were specific to e-cigarette products themselves, one of them being the current use estimate.

So that question, which was changed for the 2014 questionnaire, is now remaining consistent going forward. But there may have been some issues related to underestimation of e-cigarette use in earlier years, given the format in which the question was asked. And we think that going from 2014 forward, we have a better question that captures more use, who would have used -- who potentially have used those products.

DR. DRESLER: Okay. Is there data on the prevalence of consumers who use e-cigarettes that do not contain nicotine? So in all of your experience with all the surveys that you had up, is there going to be prevalence of consumers who use e-cigarettes that do not have nicotine in them?

MS. COREY: On the national survey data, the landscape is changing quickly with respect to questions. One place I would highlight, which folks may have seen some news about, is

Monitoring the Future, which asks a question about e-cigarette use as well as the content of what is in the e-cigarette liquid, trying to understand the extent to which nicotine versus non-nicotine liquids are being used by e-cigarette users.

I would say that this is a really evolving and challenging type of behavior to understand and get at, and we're interested in methods, questions, and development to get a better handle on what the substances are in the e-liquids that youth as well as adults are using.

DR. DRESLER: Okay, I'm not seeing any other questions, no other ones coming through. Okay, so we're going to thank you very much for the presentations and for the questions. Thank you.

(Applause.)

DR. DRESLER: And it's actually time for a 15-minute break, okay? So get up and exercise out of that postprandial sinking of the blood. And so walk around a bit, and we'll come back in 15 minutes, so 10 after 2:00, please.

(Off the record at 1:58 p.m.)

(On the record at 2:11 p.m.)

DR. DRESLER: We'll go to the next and last session for

today. And we've had some questions about the slides. So if you want a copy of the slides, you need to e-mail the workshop e-mail that you've been communicating with. So after the session tomorrow, e-mail them and ask for a copy of the slides, okay? So they are not posted, but you can get a copy of the slides. And then, as we've said before, that the webinar and transcriptions will be available in the near future.

Okay, so our fourth session, Health Risks. And our first presenter today is Dr. Cindy Chang, speaking on Biomarkers of Tobacco Exposure and Potential Harm.

Cindy.

DR. CHANG: Thank you, Carolyn.

Again, I'm Dr. Cindy Chang. I am an epidemiologist in the Office of Science, and today I'll be discussing Biomarkers of Tobacco Exposure and Potential Harm.

This is an outline of what I'll be discussing today. I'll give you some background, including some definitions. I'll go over biomarkers of exposure, biomarkers of potential harm, as well as some publicly available resources.

I want to start with some background on biomarkers and why they may be important. Tobacco products are complex chemical mixtures, and the user may be exposed to a variety of

chemicals, as we've seen. Because it may take decades to understand the health impact of new tobacco products that come onto the market, biomarkers may be a useful tool to enable us to better understand potential health impacts within a shorter time frame.

If you're not familiar, here's the commonly used definition of biomarker: a characteristic that is objectively measured and evaluated as indicators of health, disease, or pharmacologic responses to an intervention. Biomarkers are often measured in a biological sample such as blood or urine.

The FDA/NIH Biomarker Working Group recently expanded this definition to include responses to an exposure in the Biomarkers, EndpointS, and other Tools, or BEST, resource that is now available online.

When studying tobacco use, the two main types of biomarkers are biomarkers of exposure and biomarkers of potential harm. In the next few slides, I'll be describing these biomarkers in more detail.

This figure illustrates the different types of measures that can be used to assess tobacco products, from the external exposure, as on the left, to the disease outcome, all the way on the right of the figure. Note that the time frame between

the two ends can be as long as several decades, as I mentioned earlier. Now biomarkers, they fall somewhere in between these two ends.

As opposed to external exposures such as machine-measured tobacco constituent yields, as discussed earlier in the chemistry talk earlier this morning, biomarkers of exposure are often referred to as an internal dose. Biomarkers of exposure are measured in biological fluid or tissue. They can be chemical or metabolites, which is any substance produced during metabolism or bodily chemical processes. Some examples include serum cotinine, which is a metabolite of nicotine, or urinary NNAL, a metabolite of NNK, which is a strong carcinogen.

Now, biomarkers could serve to measure human exposure to tobacco product constituents. They better capture changes in behavior, such as puffing behavior, that wouldn't be captured by an external exposure. For example, we now know that risks of low-yield cigarettes were underestimated because machine-determined yields of cigarettes were accepted without examining what people actually did with these cigarettes.

In 2012 CTP identified a list of chemicals that are considered harmful and potentially harmful that are found in tobacco products and tobacco smoke. These chemicals are linked

to the five most serious health effects of tobacco, which are cancer, cardiovascular disease, respiratory effects, reproductive effects, and addiction.

That same year CTP issued a guidance for the tobacco industry to test this report on 20 of the HPHCs which were selected because the testing methods were well established and widely available. Reporting included HPHCs by category of tobacco products under our authority at that time and not necessarily for ENDS. The draft ENDS guidance does have a list of chemicals that may be relevant to ENDS, but the list is only out for comment and are not considered FDA recommendations at this time.

Next, I'll be describing biomarkers of potential harm, which may provide useful information on health risks without having to wait decades for disease to develop. So I'll paraphrase the definition from the 2001 Institute of Medicine report: Biomarkers of potential harm are a measurement of an effect due to an exposure. They include early biological effects, alterations, and clinical symptoms consistent with harm. Examples include C-reactive protein as measured in the blood and pulmonary function tests.

When we're talking about health risks due to tobacco use,

clinical outcomes such as cancer, cardiovascular disease, and COPD are definitive clinical endpoints. The challenge is that they take decades to develop, and thus they're not always practical in the regulatory setting, especially for products that haven't been on the market for very long, including ENDS products. Biomarkers of potential harm could serve as intermediate endpoints for assessing health risks of new and novel tobacco products in the absence of long-term epidemiological evidence.

As stated in the draft PMTA ENDS guidance that is available for public comment, FDA recommends the use of biomarkers in studies evaluating health effects associated with a product. In the next few slides, I'll discuss some resources relevant to biomarkers and tobacco use that are publicly available.

The workshop on biomarkers of exposure was held by CTP in August of 2015. The aims were to identify approaches to selecting biomarkers for potential regulatory use, identify well-established and promising biomarkers of exposure, and identify further areas of research.

To summarize, we heard about different approaches to selecting and using biomarkers from different perspectives,

including EPA, NIOSH, CDER FDA, and tobacco research. Another session discussed how biomarkers of exposure relate to future disease risk. And there was also an overview of biomarkers that reflect chemicals across the different classes relevant to tobacco. And the last session focused on how exposure biomarkers can be used to provide information about the use of non-cigarette tobacco products, specifically smokeless tobacco and ENDS.

In this table, the list of HPHCs are on the left, and on the right are examples of corresponding biomarkers that were discussed at the first workshop. Again, these 20 are for the originally regulated products and not necessarily for ENDS.

And as you saw earlier in the chemistry talk, the FDA draft guidance on PMTA for ENDS does have a list of chemicals that may be relevant to ENDS, but the list is out for comment and not considered FDA recommendations at this time.

This past April, we held the second workshop focused on the state of the science around biomarkers associated with tobacco-related diseases, specifically CVD, COPD, and cancer, as well as new areas of research.

Some of the findings include:

- For major tobacco-related diseases, there are more

multiple pathways by which smoking causes disease. So thus, no single biomarker is likely to fully capture a clinical endpoint.

- Biomarkers of potential harm can be further evaluated by leveraging existing studies with available biosamples or biomarker data, including cross-sectional, case-control, prospective cohorts, intervention, and smoking cessation studies.

- Many of the smoking-related diseases share some of the same pathways and biomarkers, such as inflammation and oxidative stress.

Finally, there are many available resources on biomarkers and tobacco, including authoritative reports, some of which are listed here.

In summary, I've described what biomarkers are and how they may be useful for evaluating health risks of tobacco products. I've also shared some of the existing resources that are relevant to this area and available to the public.

Thank you.

(Applause.)

DR. DRESLER: Okay, our next presenter will be Dr. Jeannie Limpert from the Division of Individual Health Sciences, and

she will be presenting on Health Outcomes.

DR. LIMPERT: Thank you, Carolyn.

Good afternoon. My name is Jeannie Limpert, and I am a medical officer in the Office of Science at the Center for Tobacco Products.

So in my talk I'll describe some background, discuss the use of nonclinical data, discuss published literature and datasets, and describe clinical investigations of health risks.

The draft guidance on PMTAs for ENDS, available for comment, states: "Your PMTA should provide data that adequately characterizes the likely impact of the new tobacco product on the health of both users and nonusers of tobacco products in order to support that marketing the new tobacco product would be appropriate for the protection of public health."

Examples of types of data that may be useful in this regard include information about user health risk and disease incidence and assessments of the health effects in users and nonusers of the product.

As discussed by our nonclinical experts, nonclinical data relevant to specific constituents delivered to the user and nonuser may provide information about the impact of the health

of users and nonusers of the tobacco product.

Aerosol constituents may vary depending on the e-liquid and the aerosolizing apparatus. Aerosol constituents for which nonclinical data may provide information about health effects include, but are not limited to, propylene glycol, glycerin, nicotine, flavorings, and metals.

In addition, as discussed by Dr. Lindsey, FDA has stated that in some cases it may be possible to support a marketing order for an ENDS product without conducting new clinical studies looking at health outcomes.

The draft guidance on PMTAs for ENDS states, "If there is an established body of evidence regarding the health impact of your product or a similar product that can be adequately bridged to your product, these data may be sufficient to support a PMTA." Examples include data from the published literature and government-sponsored databases.

If you're relying on published reports to support your PMTA, you may wish to identify why the data from those reports can be bridged to your product and are appropriate for determining the impact of the new tobacco product on the U.S. population. For published studies concerning investigations that have been conducted to show the health risks of your new

tobacco product, you may wish to provide full articles for each study and a bibliography for the studies.

Per Section 910(b)(1)(A) of the Food, Drug, and Cosmetic Act, a PMTA "shall contain full reports of all information concerning investigations to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products."

A literature review could identify health risk information available from investigations of your tobacco product or similar products and provide information to help determine the risks associated with your product as compared to other tobacco products. And you may wish to refer to the prior presentation by Dr. Christensen when developing, conducting, and presenting your literature review.

The draft guidance on PMTAs for ENDS states, "FDA recommends including studies, other scientific evidence, or both, that identify biomarkers of exposure, biomarkers of harm, and health outcome measurements or endpoints."

Health effects data related to tobacco product exposure may include changes in physiologic measurements such as heart rate and blood pressure; changes in lung, cardiac, and metabolic function; adverse experiences; and changes in

laboratory values.

As discussed by Dr. Chang, you may wish to include studies, other scientific evidence, or both, that identify biomarkers of exposure, biomarkers of harm, or both.

Section (d)(2)(A) of the draft guidance on PMTAs for ENDS states that the comparisons of the health effects of your tobacco product to other tobacco products on the market could be included in a PMTA. This will be discussed in more detail in a subsequent talk by Dr. Chen.

The human health impact should be assessed in both users and nonusers. Considerations in addressing the human health impacts of a new tobacco product in users could potentially include those who switch from other tobacco products to the new tobacco product; users who, after adopting the new tobacco product, switch to or switch back to other tobacco products that may present higher levels of individual health risk; users who use the new tobacco product rather than cease tobacco use altogether; those who use the tobacco product rather than an FDA-approved cessation medication; and users who use the new tobacco product in conjunction with other tobacco products.

Considerations in addressing the human health impact of a new tobacco product in nonusers could potentially include:

youth, never users, and former users who may initiate or relapse with the new tobacco product; nonusers who experience adverse health effects related to exposure to the new tobacco product; and nonusers who, after adopting the new tobacco product, may switch to other tobacco products that may present higher levels of individual health risk.

While there are no current requirements for CTP, experience from other centers may be useful to applicants. In other centers, FDA recommends that clinical studies to support new applications for products, such as drugs, biologics, or devices, should provide clinically meaningful, statistically valid and robust findings; protect the rights, safety, and welfare of human subjects; and are conducted in accordance with ethical principles acceptable to the international community.

The draft guidance on PMTA for ENDS states, "FDA recommends that when you conduct studies, you should ensure to the extent possible, that the study findings are generalizable to the population of U.S. users and nonusers of your new tobacco product."

In conclusion, based on statutory requirements, it is important that a PMTA provide data that adequately characterizes the likely impact of the new tobacco product on

the health of both users and nonusers of the tobacco product. New clinical studies evaluating health outcomes may not be needed to support a PMTA if there is sufficient nonclinical and/or clinical information available in the literature to characterize the likely impact of the proposed product on the population as a whole. Examples of data that could support the impact of a tobacco product on health in a PMTA may include nonclinical investigations of constituents, data in the public domain (both nonclinical or clinical), and health outcomes data of your product or similar products.

Thank you.

(Applause.)

DR. DRESLER: Okay, our next presenter is Dr. Ii-Lun Chen, who is the Director of the Division of Individual Health Science, and will be speaking about Comparator Products.

DR. CHEN: All right, last talk of the day, so please bear with me.

My name is Ii-Lun Chen, and as Carolyn mentioned, I'm the Director for the Division of Individual Health Science, and I'm going to talk to you about comparator products.

So I'll just go over some background information, talk about some potential comparator tobacco products to consider,

talk about some risk comparison using the Swedish Match North America example, and I'll finish with talking about some PMTA resources you can consider.

So as a reminder, applicants submitting a PMTA must include the information required by Section 910(b)(1) of the Food, Drug, and Cosmetic Act. This section states that an application shall contain "full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products." In simplified terms, this statement states applicants must submit any health information they are aware of, or should reasonably be aware of, about their tobacco product and comparative risk to other tobacco products.

Furthermore, the statutory authority mandates us to consider the population as a whole when regulating tobacco products. This is a powerful regulatory authority in the effort to decrease the morbidity and mortality from tobacco use.

Under Section 910(c)(4), FDA's decision must be based upon considering the health risks and benefits to the population as

a whole, including both users and nonusers of tobacco products.

So what are questions related to considering the population as a whole? Based on information submitted by the applicant, FDA must take into account the likelihood that users of tobacco products will stop using tobacco products, and the likelihood that those who do not use tobacco products will start using tobacco products.

One of the many outstanding public health issues related to ENDS that requires study is the effects of dual use, especially dual use of cigarettes and ENDS products versus exclusive use of ENDS products. As it is known that there is uptake of ENDS products by previous non-tobacco users, it's helpful to include a discussion of ENDS health impact as compared to no tobacco use. Use of publicly available literature and/or specific studies conducted on proposed products can support a PMTA.

When discussing the impact on nonusers, secondhand and thirdhand exposures can be considered. Secondhand smoke is the smoke and other airborne products that come from being close to burning tobacco products such as cigarettes. ENDS products are different from cigarettes in that they do not produce sidestream smoke, which is the smoke which goes into the air

directly from a burning cigarette, cigar, or pipe. However, ENDS users do inhale mainstream aerosol and then exhale into the environment.

Thirdhand smoke is generally considered to be residual nicotine and other chemicals left on a variety of indoor surfaces by tobacco smoke or, in the case of ENDS, left by the exhaled aerosol. Studies show that thirdhand smoke clings to hair, skin, clothes, furniture, drapes, walls, bedding, carpets, dust, vehicles, and other surfaces, even long after smoking has stopped. Infants, children, and nonsmoking adults may be at risk of tobacco-related health problems when they inhale, ingest, or touch substances containing thirdhand smoke. Thirdhand smoke is a relatively new concept, and researchers are still studying its possible dangers and, similarly, for thirdhand ENDS aerosol exposures.

So to wrap up considerations on public health risks as discussed in the draft guidance on PMTAs for ENDS, which is available for comment, there are potential benefits and risks to use of ENDS products. It is important for FDA to be able to understand how consumers and others are impacted by the availability of your product within the world of available tobacco products. Various examples on types of comparator

tobacco products will be presented in the next few slides, which may assist as part of the discussion on describing impact of a proposed product on population health.

FDA anticipates that many PMTAs will involve ENDS products. ENDS products include both the e-liquid and aerosolizing apparatus, commonly referred to as the device, whether they're sold as a unit or separately.

In the draft guidance on PMTAs for ENDS that is available for comment, it states that a PMTA "include a comparison of the new tobacco product to a representative sample of tobacco products legally on the market."

So here is a graphic broadly describing the tobacco product market. Within the sphere of all marketed tobacco products, we have a portion of products which are newly deemed tobacco products. Among those, we have the ENDS products, and within that broad class of products, you have your proposed ENDS product.

The tobacco product market can be considered in many ways. Applicants may want to consider what are the most appropriate comparators from various tobacco products on the market.

Another consideration is comparison among broad ENDS products. Among aerosolizing apparatus examples of variation

are disposable, rechargeable, cigalikes, tanks, mods, among other examples.

Example: ENDS e-liquid comparisons that may be considered are flavored versus non-flavored, various nicotine concentrations, propylene glycol versus vegetable glycerin or other bases that are used. As an example, if a manufacturer is interested in developing a 4.5% nicotine concentration e-liquid, it would be helpful to provide justification and rationale as to why such a product would be appropriate, considering most e-liquids available are in the range of 0% to 3.6% nicotine concentration. The range of nicotine concentration of e-liquids available on the market can be readily obtained via reviewing websites selling e-liquid and publicly available articles related to ENDS products.

Another example would be a manufacturer who's interested in marketing a particular base combination. They may want to compare their base combination to what is typically available on the market, which is usually a ratio of PG and VG. If other compounds are used as a base, then justification and rationale for that difference would be helpful in evaluating the product. Again, review of websites selling e-liquids and evaluation of publicly available articles related to e-liquids provide

information on common bases used for ENDS products.

So FDA understands that you may want to discuss certain topics in your PMTA, such as toxicology and health risks, with scientific data on tobacco products other than the proposed PMTA product. Whether this information is appropriate depends on the specific products, the facts of the study or data, and the appropriateness of the comparison being made to your PMTA product. You should provide justification in your PMTA regarding why using evidence or data from other products to support your PMTA is appropriate based on these factors and other relevant considerations.

In this first example from a recent PMTA submission which received marketing authorization, Swedish Match North America compared their snus product manufacturing process to that of other types of smokeless products to demonstrate how their specific processes decrease toxicological risk in their products.

Furthermore, chemical analyses of their products were compared to chemical analyses of other smokeless tobacco products on the market, and based on these analyses, it was determined that the carcinogens NNN and NNK as well as other HPHC levels were lower in their product in comparison to other

smokeless tobacco products on the market.

Other product comparisons to smokeless tobacco products discussed include, but are not limited to, nicotine levels, nicotine pharmacokinetics, use behavior, perception and acceptability. For example, they discussed that nicotine levels contained, and the dose response of their snus products were within, the range of nicotine and exposure levels found in other marketed smokeless tobacco products.

Health risks faced by Swedish snus users were compared with those faced by cigarette smokers and nonusers. Specifically addressed were issues such as risk of developing respiratory diseases (that is, COPD, emphysema, chronic bronchitis) and certain cancers (such as oral, esophageal, and lung) in Swedish snus users as compared to cigarette smokers. They discussed risk of dual use as well as Swedish snus use compared with quitting completely or nicotine replacement therapy use.

So there is available information on ENDS products that is publicly available. Examples of available information on ENDS products are range of nicotine concentrations on e-liquids as discussed earlier, general ingredients in e-liquids, packaging information, and labeling information.

Finally, I wanted to mention places where you can find additional information that can assist you in putting together your PMTA submission. I have listed in this slide several sources that may be helpful. Consider, for example, using sources such as the Surgeon General Report. I have here a few recent examples relevant to tobacco use.

And then additional resources include the National Cancer Institute Tobacco Monograph Series, the Tobacco Atlas, the International Agency for Research on Cancer handbooks, FDA electronic cigarette workshop series that were conducted in 2014 and 2015, and then the Swedish Match North American snus PMTA technical project lead review is available to the public as well. And then there is publicly available scientific literature, as discussed earlier, for example, PubMed.

And that's it. Thank you very much.

(Applause.)

DR. DRESLER: So we'll have people come up. So again, be writing your questions, and I have two.

So does FDA agree that short-term clinical studies measuring ENDS effect on respiratory and cardiovascular physiological endpoints or parameters, that would be informative? So does FDA agree that short-term clinical

studies with the effects on respiratory or cardiovascular physiologic endpoints or parameters would be informative for the review?

DR. LIMPERT: So there are no required studies, but if there are short-term studies that characterize the health impact of a tobacco product, then I would say that would be informative.

DR. DRESLER: Okay. And the second part to that question: Will longer-term measures of lung and cardiovascular cancer parameters be informative for demonstrating the appropriateness of ENDS products for a public health perspective? So longer-term studies, would they be informative?

DR. LIMPERT: So I have a similar answer; there are no required long-term studies. But again, if it does better characterize the health impact and the long-term health impact of that tobacco product, then I would think it would be informative.

DR. CHEN: And I just want to clarify too, though, that when we say they're not required, we really don't have expectations that such long-term studies need to be conducted in order to submit your PMTA and get a successful marketing authorization.

DR. DRESLER: So, Dr. Chen, this one might be for you. In evaluating the full population risk of an ENDS product, is a combustion cigarette a proper control or comparator?

DR. CHEN: I think that the health risks of tobacco products certainly can be an appropriate comparator. It depends on what you're trying to discuss. But again, because many ENDS product users are cigarette smokers or former cigarette smokers or dual users, that talking about the health impact of cigarette use is appropriate.

DR. DRESLER: Okay. How about this one then? I think this is also for you. Why can't you give us specific requirements or recommendations for what is needed for a PMTA?

DR. CHEN: So I completely understand that it would be nice for us, FDA, to have a list of all the types of information and required studies in order to have a successful PMTA. First of all, we can't do that because every PMTA is going to be slightly different. You may be talking about a part, a component, or you may be talking about an apparatus or an e-liquid or a combined product.

But in any case, what we currently have are statutory requirements. We have the Food, Drug, and Cosmetic Act. And the law, at this point, just talks about the types of

information that you have to submit. For example, it says you need to submit full statements of ingredients, you know, your manufacturing process. You need to talk about the likelihood of impact on initiation and cessation. So there are requirements in the law, but the law does not go into specifics on the studies that you have to conduct in order to provide that information.

Other requirements, if FDA was to impose requirements, we have to go through comment and rulemaking, and that's a pretty intensive and prolonged process. And so that has to happen before we can develop regulations, and at this time we don't have any PMTA regulations.

And we've iterated over and over that the draft guidance is available for comment, and Colleen Lee talked a little bit earlier this morning, the fact that the draft guidance has to go through a comment period, and it has to be finalized before it can be formal FDA recommendations.

So that has not happened at this time, and so what we're providing are general principles and information and explanations so that you can understand the draft guidance better to provide further comment, as appropriate. But until guidances, draft guidances are finalized, they are not FDA

formal thinking and final recommendations.

DR. DRESLER: Okay. During a previous FDA webinar, it was mentioned that a "sample PMTA" would be available. Is this still in the works? And two things that I'm thinking of. One, you had mentioned the PMTA in your presentation, but also we had the question earlier about a predicate product. So I'm not sure when they said a sample PMTA. Do you want to answer both, the predicate product and/or the Swedish Match PMTA?

DR. CHEN: So we are not aware of any specifics on a predicate product, and there is also no example form for a PMTA that we can provide. We do have the Swedish Match North America example. And as I mentioned, that project, the technical project lead review is publicly available, and that really goes in depth as to the thinking behind recommending and authorizing that product.

So I think that that can provide some insight into how we approached a PMTA submission and marketing authorization. But in terms of a specific PMTA example of how to submit the information and what kinds of materials go into a specific PMTA, no, we don't have that.

DR. DRESLER: Okay. Is FDA aware of public data or studies which may have been inadvertently omitted from a

specific PMTA? So will FDA note that information in a No Marketing Order or A/I letter? So apparently the U.S. Patent Office will indicate relevant prior art. So if there is a No Marketing Order or A/I letter, will the FDA say you didn't refer to these particular articles?

DR. CHEN: I'm not aware of making any such information available at this time.

DR. DRESLER: Okay. What are differences between health outcomes and other requirements regarding health risk? So what are differences between health outcomes and other requirements regarding health risk?

DR. CHANG: I'm not exactly sure what they're referring to, but if you're asking what's the difference between maybe biomarkers and the health outcomes, I can address that.

DR. DRESLER: Yeah. So I'm not sure because that is the question that I have. So whoever wrote that might want to expand that more. I'm thinking that we entitled this section called Health Risk and -- but within it you addressed health outcomes because it's -- and Kimberly, I'm looking at you, too. They're sort of the same thing, whether they're health risks or health outcomes. They're just a different way of phrasing it.

DR. CHANG: Yeah, I think they've been used

interchangeably.

(Off microphone comment.)

DR. CHANG: Yeah. And many things can reflect health risk. I mean, that's kind of a broad term.

DR. DRESLER: Okay. All right, we might get some follow-up on that.

With respect to the HPHC list, does data showing the absence of one or a number of HPHCs for e-liquids versus traditional tobacco products, such as cigarettes, provide a framework for a reduced-risk argument for ENDS, especially if the missing HPHCs are known to be connected to a significant biomarker? So with respect to the HPHC list, so if one or more of the HPHCs are lower in the e-liquids as compared to, say, a cigarette, does that provide the framework for the argument for reduced risk for ENDS?

DR. CHEN: Yes, it can.

DR. DRESLER: Okay. How can I study the impact of ENDS on youth initiation if I do not specifically conduct a study with youth? How can I study the impact of ENDS on youth initiation if I do not specifically conduct a study with youth?

DR. CHEN: So there may be studies on young adults, for example, and you may be able to bridge, using that information,

to the youth population. So this is something I think we'll go more into in Day 2, but -- so hold on to that question, and we can expand a little bit more.

DR. DRESLER: Okay. Other questions online or in the room? I think I have one more coming. No, two more coming up. Otherwise, everybody else in the room has got them all answered because this is like your last chance for today. You can think about it overnight and bring in the questions tomorrow.

I'm sorry, we're done. That's it, there are no more questions?

(Off microphone comment.)

DR. DRESLER: Oh, there's one more being written. Okay. No pressure, sir.

(Laughter.)

DR. DRESLER: So, again, if you want a copy of the slides, e-mail the workshop e-mail that you've been communicating with before and ask for those. Say which ones that you want, and you'll get them as a PDF, not as a PowerPoint slide. They'll come to you as a PDF. The transcripts and the webinar will be available online, and that usually takes a couple weeks to get that transcript done because we review it to make sure that it's the same what was said here. And maybe taking my jokes

out of it, I'm not sure.

(Off microphone comment.)

DR. DRESLER: Yeah. No, unfortunately those -- they'll be there on the webinar. We'll try and get those out of the transcript as we see whether that's coming up.

We might be able to beat the rush hour traffic, which is a good thing, by finishing a little bit -- the answer is no, we won't beat rush hour traffic. So if you're new to the D.C. area, I don't know if there is such a thing as beating rush hour traffic.

(Off microphone comment.)

DR. DRESLER: Or any of them. One question coming up. No questions coming up.

Okay, so there are a couple of hands raised over there. I somewhat feel like an auctioneer, you know, over here, over there. We do want to make sure we get all the questions answered that we can.

So more news. Tomorrow starts at 8:30. I try to start on time, particularly the first one in the morning, so please do come in on time.

Those are all the questions that we have. Okay. Sometimes questions come in, and they're more pertinent for the

next session. I had a couple of those, and we'll get those answered tomorrow. So we have no more questions.

Thank you, panel, very much. And thank you, everyone. We'll see you tomorrow morning.

(Applause.)

(Whereupon, at 2:59 p.m. the meeting was continued, to resume the next day, Tuesday, October 18, 2016, at 8:30 a.m.)

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 17, 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.

_____

ED SCHWEITZER

Official Reporter

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