UNITED STATES FOOD AND DRUG ADMINISTRATION

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DEEMED TOBACCO PRODUCT APPLICATIONS:
A PUBLIC MEETING

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MONDAY
OCTOBER 28, 2019

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The public meeting met at the FDA White Oak Campus, Great Room, Room 1503, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:30 a.m., Anne Radway, Moderator, presiding.

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PRESENT:

ANNE RADWAY, MS, Moderator; Office of Science, CTP
CRYSTAL ALLARD, Office of Science, CTP
SARAH AMYOT, MPH, Office of Science, CTP
KEVIN BURD, North America Nicotine
CHAD BURGER, MS, Office of Compliance and Enforcement, CTP

EMILY BUSTA, MS, Office of Science, CTP

PRISCILLA CALLAHAN-LYON, MD, Office of Science, CTP

LEANNE CAMPBELL, PhD, RAI Services, Co.

DAVID GRAHAM, MPA, NJOY

MATTHEW HOLMAN, PhD, Office of Science, CTP

OUIDA HOLMES, MPH, Office of Science, CTP

ANUSCHKA MERSON, MS, ITG Brands, LLC

MICHAEL OGDEN, RAI Services, Co.

LILLIAN ORTEGA, MPH, Office of Compliance and Enforcement, CTP

STEPHANIE REDUS, MS, Office of Science, CTP

CHRISTINE SABA, MPA, MPH, Office of Science, CTP

CRISTI STARK, MS, Office of Science, CTP

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

8:37 a.m.

DR. HOLMAN: Well, welcome to all those in the room, as well as the many folks who are viewing remotely. As you know, we held one of these meetings last year, focused on application review. We were looking last year to really supplement our different means of communicating with stakeholders around application review.

And so we tried this two-day meeting last year. I think my staff, my colleagues at FDA found it very useful, as a very useful tool in communicating with stakeholders around application review. We received a lot of positive feedback from stakeholders that they felt like they got useful information during that two-day meeting.

So we decided to hold a similar meeting this year as well. Obviously, with all the issues around deemed products, we decided to focus the next two days around deeming, and what

that means in terms of application review.

I want to thank all those who have signed up to participate either in person or remotely. I also want to thank all my colleagues at FDA for all the work they've put in, pulling together a lot of what I hope will be very useful information for all those in attendance.

I think I would just really like to encourage stakeholders, both in the room -- we will be using, handing out cards. We can ask questions and those viewing remotely will have an opportunity to ask questions electronically as well. I just encourage you guys to ask a lot of questions. We've intentionally left in a lot of time for panel discussions today so that there was an opportunity to ask questions.

This is really your meeting to ask us questions, to get information that you need. We tried to anticipate the type of information you guys would want and include that in our presentations. But we're fully aware that we may not anticipate all the questions, and again I

would encourage you guys to please be active in asking us a lot of questions. We're here to try to answer those questions for you, and we can only do that if you guys are asking us questions.

So welcome. Thank you for your attention over the next two days, and thank you for being willing to ask us questions and actively participate and engage in this dialogue. With that, I'm going to ask David Graham from NJOY to come up and just say a few words. Thank you.

MR. GRAHAM: Thank you, Martin. Good morning, everyone. I'm David Graham, Chief Impact Officer at NJOY, and I want to first thank you Matt for the invitation to speak here, and also to your colleagues in the Office of Science for organizing this meeting.

The program you set out here looks extremely comprehensive, and I'm sure is going to be highly appreciated by the many participants here in the room, as well as those joining by webinar. I expect everybody's going to be

watching and listening very carefully as they continue to piece together invaluable information to help address CTP's expectations for premarket submissions, especially PMTAs.

Development and execution of a program leading to PMTA submission is no small challenge, especially for ENDS, given this is the first time for everyone in the category. For what amounts to several years now, we've needed to make progress with some uncertainty while awaiting FDA's final guidance for ENDS, PMTAs and the PMTA proposed rule.

But these documents are out now. We've all read them very carefully, and expectations are clearer than before. Yet for many the need to calibrate the scope, the scale and the spend of the PMTA programs is likely still an ongoing challenge. The more extensive the program, the higher the cost and usually the longer it takes. There needs to be high quality, but costs and time aren't boundless.

While there might be various

perspectives on the right-sizing of a PMTA, I expect we can all agree that it need neither be extravagant nor mediocre, and should be fit for purpose somewhere in between the two. In other words, not too much, not too little, just right. Some may think of that as the Goldilocks scenario.

I lived in Sweden for some years, and I think the Swedes have a word and I can't say it, for that which describes that concept well. That word, which doesn't directly translate in English, is lagom. Lagom may be translated using several words such as enough, sufficient, adequate, just right, in moderation, in balance and suitable. But some of these and everyone might suggest some scarcity, but lagom is really got the connotation of appropriateness. It's good, it's right.

Now those of you that have been in dialogue with the FDA, you'll recognize and I hope that you'll see that they use the word appropriate a lot. Appropriate and also the word

reasonable, and that's really where we're heading for here.

I trust that these next two days will give an invaluable opportunity to hear from the team, the CTP team on their latest perspectives, and what they consider is reasonable and appropriate in applications that have real potential to meet the standard of appropriate for the protection of public health.

I'd like to thank the Office of Science for preparing for what promises to be a very interesting two days. Many of the presentations I'm sure will cover much of what's written in the guidance, but the very interesting parts of these meetings are often driven by the questions that people ask. I really encourage everyone to take advantage of this opportunity.

Time is not so far from compliance dates, and this is a golden opportunity to start asking questions between the lines. I'm really looking forward to that and looking forward to the engagement, so thank you very much.

(Applause.)

MS. RADWAY: Good morning and welcome. My name is Anne Radway. I am the associate director in the Division of Regulatory Project Management in NCTP's Office of Science. I'm going to be one of your moderators over the next two days, along with Dr. Todd Cecil, the associate director in the Division of Product Science.

Thanks to Dr. Holman and Mr. Graham for the welcome and opening remarks, and thank you to everyone again for being here. I plan to go over some logistics first, and then an overview of the meeting including the purpose and some expectations.

So first things first. We'll have one break this morning before lunch and then we'll break for lunch around 12:15. A box lunch is available for purchase. You need to get the form in the lobby at the table, and then bring that form to the kiosk around this corner to purchase your box lunch.

One other thing I wanted to mention is

that our room configuration is going to be different for the two days. So we want you to be aware that tomorrow the room will be much, much smaller, but we did keep registration numbers down to accommodate that smaller room. And then lastly the recording of both days, along with the transcript, will be posted on the CTP website sometime after the meeting.

So this meeting is intended to provide information on the agency's expectations for tobacco product applications, with a particular focus on deemed tobacco products. One of our goals is to continue to increase transparency in advance of the court-mandated submission deadline of May 2020, by not only giving more information on the application process but also by presenting reviewer perspectives and lessons learned in the evaluation of the applications we have reviewed up to this point.

FDA does not intend to address or discuss anything outside the scope of this meeting. For example, pulmonary illnesses

related to e-cigarettes, THC or marijuana, any pending litigation or future rulemaking, or potential enforcement discretion policy for deemed products. So again, these topics are outside of the scope of this meeting.

The presentations will include product review policies, procedures and general scientific principles. Our goal is that this information will improve understanding and assist with the materials and resources that are out there for those considering submitting applications.

FDA has recently released or finalized proposed rules, guidances, technical specifications, memos and other information to provide as much information as possible. These lay out our expectations and the processes used in the review of premarket applications. Some of the speakers will provide updates and perspectives on the documents and their experiences, and each of their presentations represent their particular perspective and

experience, but are not statements of FDA policy or regulation.

So following each presentation, each session of presentations, we will conclude with a panel discussion, including representatives from industry and FDA. Questions or clarifications will not be answered by the presenters, but rather addressed during the panel discussions. Therefore, we encourage everyone to utilize the note cards being passed around to write down those questions.

There are also note cards available at that back table, if you need a note card. Please ensure you clearly communicate what you want to ask and make sure you write as neatly as possible. At the start of each panel discussion, each panelist will have up to and no more than five minutes to introduce themselves, excuse me, and provide remarks on the session topic.

We will time those remarks and we ask that panelists stick to this time. Again, please ensure your questions are related to the scope of

the meeting and pertain to the topic of that session. If your question does not get answered or you have additional questions, you can submit those questions to askctp@fda.hhs.gov. Lastly, FDA understands the time limitations now on industry to submit, and on us to review, deemed tobacco product applications, and we hope this meeting will provide resources that will lead to better applications to meet those goals.

So now we will start with Session 1, Communication and IT Resources. The first presentation will be on the CTP website by Ms. Stephanie Redus, followed by Ms. Crystal Allard, discussing an overview of electronic submissions. Ms. Redus.

MS. REDUS: Good morning and welcome. My name is Stephanie Redus, and I'm a senior regulatory health project manager in the Office of Science. Today, I will be discussing the CTP website and what's new. I will be covering what has changed with the website, featured information and content, some new site pages and

updated pages, and also how to contact CTP.

The CTP website contains information for tobacco products, application submission, regulatory information and a variety of other useful information. Recently, CTP has redesigned the website, but don't panic. The overall structure and content has not changed. So let's discuss what has changed.

With the recent update and redesign of the CTP website, we have changed the platform that the site has been designed on. We understand that many of you travel and access the website from various devices. This was done to ensure all users have quick and easy access at their desk or on the go with their mobile devices, and it will enhance your user ability on those devices.

This platform can handle content in a way that makes it easily accessible and shared on many platforms that our audiences utilize. Is that better? For example, websites and mobile devices. It is also compatible with social media

platforms such as Twitter, Facebook, Instagram and various other applications.

This new platform establishes a foundation for future enhancements. It also meets new federal, Health and Human Services and FDA requirements. This will allow updates to be done quicker and easier, as CTP routinely updates the website as needed to maintain current information. With this new platform, it will enhance user ease of navigation. It adopts a mobile first responsive approach.

This was based on review of web analytics and internal and external user experience sessions. CTP conducted research to better understand how visitors interact with our website. This website has been designed to be more user-friendly, with content discovery to be a more show-and-tell perspective.

We're utilizing more images, along with visual elements and short descriptions. Different users use different devices. In the past, a view on the computer would be different

versus a mobile device. Now with the recent changes, they are very similar. As you see here, on the right is a mobile view; on the left is a desktop view.

The information layout displays have changed. First is our featured articles. This is an article that is being featured for a period of time and routinely changes. Next is the latest updates for the Center. This includes recently featured articles and news stories. Finally, the Tobacco Products Section, which contains essential information for the Center.

So now let's discuss the featured content and organization of the site. Let's review the Tobacco Products Section of the website. This area is an important area to visit, as it contains information that will assist you in preparing applications and submissions along with compliance.

I will highlight the organization of the featured content. The content and overall structure of the new site is exactly the same.

The links are all the same and will take you to the most current information available. There are seven main buckets of information in this section, starting with Products, Guidance and Regulations; Compliance, Enforcement and Training; the News Room; Public Health Education; Science and Research; and About the Center for Tobacco Products.

We will begin to look at them in depth shortly. Let's start with the Products, Guidance and Regulations page. The first section on this page contains information about the various categories of tobacco products. The next section of the page is for guidances. The next is regulations, then the manufacturing of tobacco products and additional resources. We will look at each of these sections in depth in the following slides.

I would also like to point out from the side menu that it contains links to various other information. It will be different on each of the pages. I would like to point out how you

can submit comments to Tobacco Products. So let's take a look.

On this particular page, you can submit comments to various proposed rules such as the proposed tobacco products required warnings for cigarette packages and advertisements, or open modified risk tobacco product applications. Here, you can see that we have an open MRTPA for VLN trademark King, BLN trademark Menthol King combusted filtered cigarettes.

Also on this page, you will find information to aid you in submitting comments, such as what makes an effective and useful comment, and additional tips for submitting effective comments. Also, the regulatory process steps. What is your role in shaping tobacco regulation? A proposed rule or regulation is published in the Federal Register. Then the public will have an opportunity to submit comments. This period is typically 60 to 90 days.

Then the FDA considers comments and

issues a final rule. Once implemented, retailers and businesses comply with the regulation. So let's take a look at the Tobacco Products required warnings for cigarette packages and advertisements rule. This rule was published August 16th, 2019, and is currently closed for public comment. It closed on October 15th, 2019.

So let's take a look at the marketing distributing tobacco products page. We can easily navigate from here. Looking at the information located on the market and distributed tobacco product page, it introduces you to what a new tobacco product is and grandfathered tobacco products, along with the three pathways to market a new tobacco product. I will be covering the pathway pages in more detail later in the presentation.

So let's go back to the Products, Guidance and Regulations page, and let's take a look at vaporizers, e-cigarettes, hookah pens and other electronic nicotine delivery systems page. On this page, you will find specific information

on ENDS products such as statistical information. The next section is the regulation of ENDS. Here you can see some examples of ENDS products. Next is information about the manufacturing of ENDS and the required nicotine addictiveness warnings on packages and advertisements.

Then you will find retail sales of ENDS and information from vape shops that mix e-liquids or modify products, importing of ENDS and finally anyone can report an adverse experience or potential tobacco product violation. Also, if you believe products are being sold to minors, you may also report this potential violation here.

Each of these product category pages contains a significant amount of information about the tobacco products. I have only covered one category. We recommend you review each of these category pages in detail.

So let's take a look at the information under the Guidance page. This contains a list of guidance documents that the

FDA has issued. These are listed in the order that they were issued, with the most recent one being listed at the top and identifies the type of guidance. You can click on the title to open it and review.

So let's take a look at the most recent finalized guidance we have issued, which is the premarket tobacco product applications for electronic nicotine delivery systems, ENDS, which was issued June 11th, 2019. This guidance is intended to assist persons submitting premarket tobacco product applications, PMTAs, for electronic nicotine delivery systems, ENDS. You can also submit comments to the guidance at any time using the link shown here.

We recommend that you review all these guidances in detail, as they contain significant information for compliance.

Next is the Regulations Documents page. This page contains a list of rules and regulations that the FDA has issued. It includes Advance Notice of Proposed Rulemaking, proposed

and final rules. These are listed in the order that they were issued, with the most recent one listed at the top. You can click on the title to open it and review.

Let's take a look at the most recent proposed rule we have issued, which is the premarket product, tobacco product applications and recordkeeping requirements, which was issued September 25th, 2019. This rule is intended to set forth requirements for PMTAs and would require manufacturers to maintain records, establishing whether tobacco products are legally marketed. This proposed rule is currently open for comments. You can submit comments until November 25th, 2019.

The Manufacturing Tobacco Products page contains a significant amount of information, starting with how to comply with FDA's tobacco regulations, information about user fees and how to pay them. It includes information for registering your establishments and submitting a list of products, including

labeling and advertisements.

Please note what is displayed is not a complete list of items. Please refer to the website for a complete list. It also contains information how to submit health documents, ingredient listings, warning plans, harmful and potentially harmful constituents, HPHCs, how to submit an application. There are also resources for electronic submissions, which you will hear more about later today. This information will help you to prepare your submissions and applications. This concludes the Products, Guidance and Regulations pages.

So let's take a look at the Compliance, Enforcement and Training webpage. This page contains information about warning letters, civil money penalties and no tobacco sale orders. It also contains compliance information for manufacturers and retailers such as retailer education, webinars and retailer training, enforcement and misbranded and adulterated NSC tobacco products; also,

manufacturer-distributor and important compliance information.

Next is the News Room page. Here you will find press releases, public meeting information and featured stories. You can click on each one of the titles to read the article. It is organized by year and month, with the most current article listed first. You will also find an archives section and additional resources at the bottom of the page.

On the public health education page, you will find current campaigns such as the real cost and Every Try Counts. You can click on each one to view the campaign information. This page also contains health information articles and information about tobacco products and their components. There is also information on the use of tobacco products and their impacts.

On the Science and Research webpage, you will find information about research news. You can also subscribe to the Spotlight on Science, where you will get email updates about

tobacco science. There are also interviews with various researchers about current tobacco science. You can also access the science, the FDA's Science Forum on this webpage.

On the Science and Research page, you will find information about CTP's key areas of focus, the Center vision, mission, job opportunities, leadership and opportunities to work with CTP. There are also several ways for you to connect with us. You can follow us on Twitter and Facebook. You can watch us on YouTube, sign up for email updates or read the latest consumer updates.

The CTP website has searching capabilities. The search feature is located on the top right corner of the webpage. It is located in this spot on every page. So no matter where you are on the site, you can search. You can search the CTP website for a specific topic. For example, you can search on PMTA. You will get a list of various links of PMTA information that can assist you in the preparation of a PMTA

application. You can search on any keyword or topic.

So now let's look at some new site content and updated web pages. Let's start with the scientific policy memorandums page, which is new. You can access it from the Market and Distribute a Tobacco Product page. This page contains various memorandums that assist CTP in evaluation of applications.

For example, the use of surrogate tobacco products and SE reports, or product quantity changes and substantial equivalents reports for statutory regulated tobacco products. This information will help to lead to a more efficient and predictable marketing authorization process for both manufacturers and the FDA. These are grouped by topic.

Information contained in these memos is subject to change based on advances in policy, regulatory framework, and regulatory science, and is not binding on FDA or the public. These memos may serve as a useful additional reference.

However, they should not be used as a comprehensive manual for preparing or anticipating review of tobacco product applications, as they represent FDA's approach at the time these memos were written.

CTP has recently updated submission and pathway pages. We have updated the substantial equivalence, exemption from substantial equivalence, premarket tobacco products, the modified risk tobacco products, and the Tobacco Product Master File pages. These pages were streamlined for consistency across the different pathways. They provide information on preparing and submitting an application or submission. Also, performance and reporting information for the pathway, if applicable, and additional resources.

So let's take a look at the PMTA page. This page contains an overview of requirements for preparing a PMTA. It includes recommended structure on how to submit a PMTA. It includes the PMTA process that Ms. Busta will cover in her

presentation. This page also contains marketing orders for PMTAs and links to resources that will assist in preparation of an application such as rules, guidances, webinars and any tools that are available.

Now let's take a look at the marketing orders for SE web page. Shown here is a general representative sample of the types of SE marketing order information available on the website. More specifically, order letters, decision summaries, environmental assessments, known as an EA, and finding of no significant impact, known as a FONSI, are posted for public viewing.

Clicking on the product name provides the SE or NSE order letter for that particular tobacco product. The order letter acknowledges scientific review completion. It explains marketing order status and reminds applicants that the new tobacco products specified are subject to the requirements of Chapter 9 of the Federal Food, Drug, and Cosmetic Act.

The decision summary, also referred to as the TPL review, captures the regulatory compliance and scientific review conclusions for that tobacco product application. Reading TPL reviews may be useful to understanding the scope and depth of CTP's application and review process, in addition to the order letter NTPL review. FDA also provides the corresponding EA to address environmental impacts that may be caused from tobacco product manufacturing, use, and disposal.

In support of an EA, a FONSI may be prepared which concludes that the marketing order for this new tobacco product will not have a significant impact on the quality of the human environment. Prior to website posting, FDA redacts information from these documents to protect confidential and trade secret information in accordance with applicable statutes and regulations.

Additionally, these documents are reviewed to ensure compliance with Section 508,

which requires that all website content be accessible to people with disabilities. For these reasons, the review time for posting may vary based on the content of each document. We also post marketing orders for the exemption of SE.

Shown here is the most recent exemption from SE orders issued. You see that the layout is the same as the SE marketing orders page. There's also a web page for PMTA orders. These are grouped by the year that they were issued. This page contains the same documents that I discussed on the SE marketing orders page. The marketing order or no marketing order, the decision summary, the EA and FONSI, as appropriate.

For PMTA, the label is also posted for the tobacco product. There is a lot of information located on the CTP website, but we understand that you still may have questions. There are multiple ways to contact us. For general questions, CTPA encourages you to reach

out to the call center phone lines. The CTP call center phone number 1-877-CTP-1373. Staff are readily available to assist between 9:00 a.m. and 4:00 p.m. Eastern Daylight Time. General questions also can be sent by emailing askctp@fda.hhs.gov.

All regulatory correspondence, including written and electronic submissions, are processed through CTP's Document Control Center, also referred to as the DCC. Here is the address. Note that delivery hours are from 8:00 a.m. to 4:00 p.m. Deliveries received after 4:00 p.m. will be date-stamped the next business day. You will hear more later today about electronic submissions.

Small businesses can face special challenges with compliance and resources. CTP has a Small Business Office that offers help to small businesses to understand and comply with tobacco regulatory requirements. If you're unable to locate information you are searching for, please reach out to our Small Business

Office. They can be reached by email, phone or by mail.

CTP also has an Ombudsman's Office, which serves as a one-stop shop for informational advice or consultation for stakeholders who have complaints or inquiries. The CTP Ombudsman's Office provides a safe space for stakeholders to voice their questions, concerns and complaints. Here is the information for contacting Mr. Nathan Hurley, the CTP ombudsman.

Please note there is also an associate ombudsman, Ms. Arielle Patano. We have covered a lot of information here today. The CTP website is a valuable tool for you to obtain information for tobacco products, submission of applications, compliance, and training.

Our goal for today was to provide you with an overview of the new and improved CTP website. We have highlighted featured content on the website, identified new site pages, and updated pathway information. I've also provided you with contact information for CTP. Thank you

for your attention and time.

(Applause.)

MS. RADWAY: Thank you, Ms. Redus. I just wanted to clarify one point that I made earlier about questions. So if you have questions for the panel discussion that you want answered during that session, you need to email workshop.ctpos@fda.hhs.gov. So again, that's workshop.ctpos@fda.hhs.gov. If you have additional questions that don't get answered during the panel and you still want those questions answered, then you can email askctp@fda.hhs.gov. Okay.

Ms. Allard?

MS. ALLARD: Thank you.

My name is Crystal Allard. I'm the director of the Division of Regulatory Science Informatics in the Office of Science at CTP. I am fairly new. I've been here for nine months now as of last week. I think I'm a fully gestated Division Director in the Office of Science now.

Though most of my colleagues in the Office of Science focus on things like chemistry and toxicology and engineering and physics and are medical doctors, in my division our mission is to bring IT solutions to the reviewers, to help them enhance and expedite their review, right?

Okay. So today, I'm going to talk to you about the various ways that we can use technology to enhance our review process, thank you. But first, I want to share that I have -- okay, hold on, I'm doing it, okay. But first I want to share that I have a bit of a secondary agenda, okay?

I love technology, and today I would like to demonstrate ways that we can use technology to interact with each other and share information. Anyone who knows me knows that I'm a huge tech nerd and I also just really like to use technology to have fun, so I'm going to try and do that today with you guys.

First, there will be a quiz. Don't

worry, it's intended to be a very fun quiz. Does everyone have their cell phone? This is the only presentation in which you are going to be encouraged to use your cell phone throughout. If you have your cell phone available now, you can start to get ready to participate in the quiz. There are a bunch of ways to do this.

You can use a browser on your phone, Safari, Chrome, Firefox, Internet Explorer if you have to, and you can just go to this link, pollev.com/crystalallar, there's no D even though my last name is Allard, 597. There's another way to participate. If you really want to download the app, you can go to the app store and download the Poll Everywhere app. You don't need to go there yet. That's what it will look like. It's up and active.

If you are participating from the webinar, you can join the poll as well. You don't need to be here in the room. Anyone who wants to participate in the poll can, okay. Keep your phones handy, we'll need them.

Okay. So today I'm going to talk about a number of ways that will help us receive electronic submissions and use them for an expedited and efficient review. One of the ways we can do that is by grouping products and submissions. I'm also going to talk about how we can organize submissions, some technical specifications for electronic submissions; that part's a little dry, sorry.

We also have some tools to help you prepare your electronic submissions, and I'm going to make sure that you know about them and know how to find them. We're going to talk about how you can submit them. We'll talk about when you can call a help desk. So if you need to phone a friend, we have a friend waiting for you to help, and then we'll have some additional resources, though Stephanie already did a pretty good job of covering them, so none of them should be new to you.

Okay. First, grouping. So if you have yet read the proposed PMTA rule -- riveting

-- you will have seen that there is a mention of how you can group multiple products into a single submission when you send it to CTP.

Just a little bit of background for folks. The HL7 is a data standards organization. They use the term grouping when they created the eCTD, when they created a regulated product submission, which is called RPS, and we're using it as part of our electronic submissions, to create our eTTD, our Electronic Tobacco Technical Document. We'll talk about that a little bit more.

So when you are grouping products into a single submission, there are a number of ways that you can do that that will really help us to use the information that you're submitting to do our review. If you have products that have the same domestic manufacturer or importer, and the same submission type, as in PMTA SE, et cetera, and the same product category, and the same product subcategory, those can be grouped into one single submission to CTP.

If there's any confusion about what each of these things mean, there are links on here. When the slides are posted, those links will be live. The links to manufacturer or importer go to our web page where those definitions exist for you to reference. The product category and subcategory link to the unique product ID memo, which is also publicly available, and describes in detail exactly what product category and product subcategory means, okay? What we're referring to there.

I also want to bring your attention to the little icon up at the top here. Yes, see? We're already doing it. See how it has a little picture of a photo up there? That's to encourage you to take a photo of this slide because it might have some information that could be in a quiz later, okay? So if you keep your phones handy, every time you see that little icon, that means take a nice photo, keep it for posterity, and also maybe reference it later. I'll give you a minute. I see people. Yep. Feel free to take

me in the photo too. I like it.

(Laughter.)

All right. So here is an example of the type of information that you could include in a submission to describe the products that are grouped together in a submission. You'll notice it's an Excel spreadsheet, pretty basic stuff. Excel is very useful and easy for us to use, so we appreciate it when you send information in spreadsheets. We like tables.

You'll see that the information is in all of the columns across the top, right? So we have product name, product type, package, package quantity, units. It's always helpful if you separate your information from your units and do units in a separate column.

This is not a full list of all of the information that we have in this example spreadsheet. The full list is here. There's not an icon on this, but I think it would be useful to take a picture of too. Here is the full list of information that would help us when you group

your products into a submission, okay? We will use this information, I promise, to help us expedite our review, to group our own reviews.

This information, having it in a spreadsheet and easily and readily available for us to pull into our review tools is incredibly helpful. Okay. So that's grouping. We're going to move on to another topic.

This one is about how to organize a submission when you're sending it to us to review. Okay. So in order to help you understand how to organize an electronic submission when you're sending it to us, we have created the Tobacco Technical Document. This helps us very much in terms of understanding where information is housed within a submission, okay?

It's based on the Electronic Common Technical Document, which is used at CDER, which is where I have worked for a long time previous to this. It takes unstructured information where you can put whatever you want wherever you want,

and puts it into a standardized structure where we have groups for administrative information, summaries, environmental impact. That's new from the eTTD, it doesn't look like the one that you would use for pharma.

So here's the standard pyramid. This is the basis of the information. The reason it's put into a pyramid is because the majority of the information that you would submit are in modules 3 through 7 down at the bottom. The middle bucket is where you would put summaries that summarize all that information.

Reviewers tend to like to start with the summaries, because it's good high-level information, and then move into the more detailed information at the bottom. The tiny top is the administrative section, also called Module 1, and I'm going to go through each of these modules in detail.

Okay. So just to help you understand why this matters, why should you care, why would anyone do this, right? It might take a little

more effort. It helps us because when we receive submissions that are not in any sort of a standardized format, they're not uniform, which means that we can't look across them and find the information. We can't know where to find information before it arrives on our doorstep, and it takes us a lot of time to get oriented to each of those individual submissions.

It also requires us to do very manual, very tedious data entry, right? Literally a person sitting at a computer typing words in. That is highly error-prone and boring. We really don't want to do that if we don't have to.

It requires manual loading and viewing of submissions with people's eyeballs. We can't use computers. It's very difficult to find information. People have search through. They have to read every single word. It's hard to notate that and share it with other reviewers, and it's difficult to reference shared product documents.

You're going to hear about master

files in-depth later on, but this is a good example. It's hard to find master files. When we create a structured submission, now we have repeatable, predictable, information. We know where to find it. The documents are named similarly. They're organized similarly, and review teams know where to find it across the review team. They can all go to the same place and find the same information.

It helps us automate data. It helps us move documents through a review process for reviewers using computers and using software, right? We love technology. So this helps us use technology. It also helps us capture and reuse submission information. This is really helpful. If you don't want your reviewers to spend their time typing in the product information over and over and over again throughout the review, we can help them with that in using software, but we need to know where to find it, and the standard submission allows us to do that.

It also provides support for group

submissions. There's a lot of information in a submission that houses many different products. It helps us find it if it's all in the same predictable place. It also helps us cross-reference previously submitted content. Someday we'll get into the full environment that is electronic and uses electronic data standards. In that environment, we can be cross-referencing information so that you don't have to keep resubmitting it over and over again. Great.

So now I'm going to move into the very specific information about the submission table of contents. I'm not going to read all of these to you. You can read them yourselves or look at the slides later. It's important to understand that we broke the submission organization table of contents into modules, right?

Each module can be followed like a folder. You can literally have a network folder and name it Module 1, Module 2, Module 3, right? So within each of those folders, you would put all of the documents in that category that are

relative, right? So in the Module 1 folder, you would include all of your Module 1 administrative information. That includes forms, et cetera, and there are seven modules in the eTTD.

So we created two new ones that didn't exist in the previous versions, the clinical product impact on population health, that's new, and environmental impact. That's also new as well.

Okay. I'm not going to read all of these to you, but in Module 1, in the second level, this where you would put things like your cover letter, your forms, labeling, correspondence, master file authorization documents, et cetera. Also yes notice, there is another little camera icon there. I will give people a minute.

All right. Module 2 is where the summaries go. It's a really handy place for you to summarize everything that's in your submission. So all of your studies can be listed here. All of your product description and

manufacturing summary high-level information can go here. If you've done clinical studies and you want to reference them at a high level, that can all go here. Your index of all of the reference literature, all of that like summary level, high-level, introductory stuff goes in Module 2.

Module 3. This is Todd's favorite module. You'll meet Todd later. This is where you can put your product description and manufacturing information, performance information, tobacco product comparisons, manufacturing, that sort of stuff.

Module 4, this is where the non-clinical information goes, right? So if you've done non-clinical studies you can do a list of all of those, your non-clinical studies, all of the results. Behavioral studies for non-clinical would also go here. You can include your non-clinical literature reviews and any 904(a) or 904(b) information. Oh sorry, I misread that. That's 911(d) and 910(b). I'm still learning the regulations, I'm not going lie.

Okay, Module 5. This is individual health in the eCTD. Formerly, this was just called clinical, right? But at CTP we're special and we have multiple kinds of clinical data, so we split it out. This is for the individual health information. So abuse liability studies, PK and PD. Actually studies, individual health literature review and again, 911(d) and 910(b) information can go here.

Okay, Module 6, population health. This is a new module, you may have never seen it before. If you haven't, if you're at all familiar with the eCTD. So this includes all of our population health information, like epidemiology studies, epidemiology, observational and behavioral. We have health risk epidemiology studies here, population modeling and analysis information.

This is all really new to me. I think it's super-exciting that we get this information and that we have folks who review it in CTP. That did not really exist so much at CDER, and so

I find it really exciting that we have a very special carve out place for epidemiology and our epidemiologists. So if you also think they're special, this is where you would put their information and they'll be able to find it every time.

Okay, Module 7. Again, a new module. Doesn't exist in the eCTD. This one focuses on the environmental impact. It includes mitigation of environmental effects information. We have alternatives to proposed actions here, right? You get the idea. We don't need to read these things. Everybody done taking pictures? Okay.

Okay, so that's the submission organization at a high level. Again, if you are going to submit an application to CTP, it is very helpful for us to have that in a predictable, repeatable, format.

And now we're going to talk a little bit about technical specifications. We have on the website a document called Technical Specifications for Submissions to CTP. It lists

all of this information and I will include a link to it too. But there are some I really want to highlight, because there are some very, like, big ticket items that help us use and review your submissions.

So again, if you've read the proposed rule, you'll see that FDA is proposing that the PMTA documents be submitted in an electronic format that the agency can process, review, and archive. You'll probably hear me say process, review, and archive a zillion times. Apologies, but it's really important to us.

In order to process, review, and archive the documents that are included in a submission, we need to make them -- we need to receive them in a usable format, right? So PDF files. We would like to receive PDF files directly from the source file. We assume the source file is Word. Please do not print out a Word document and scan it into a PDF.

If you create it directly from a Word document, then we're able to use that

information. We can index it. We can make it available to reviewers. Please include a table of contents. The submission module table of contents that we just went through, that's one, but also every document can contain a table of contents that helps us navigate them.

Working hypertext links and bookmarks. Think about your package as something that is self-contained. All of those links and bookmarks need to work within that package. So my recommendation would be that you would take that package and put it on a different computer, on a different network and test all of the links and bookmarks before you submit them, to make sure that they work somewhere else. Because what happens is, in the transmittal process, they get broken. So you have to make sure that they work in that self-contained little package.

This one's fairly obvious. Legible, English language content or translations, thank you, and electronically readable valid FDA form. Straightforward.

Okay. So we have to talk a little bit about integrity and security. I don't work in the FDA's centralized IT group, but they are very serious about the types of documents that we receive here, and they require that we have some standard set of rules that are for the entire agency, not just CTP.

So in some cases don't submit damaged media, right? If your CD is broken, we can't read it. If your flash drive doesn't work, we can't use it. So again, test it in multiple places. Virus scanning. This is obvious. Do a virus scan of your media before you submit it. If we get something with a virus, we just can't open it, right? We'll get in big trouble if we try.

Avoid security settings. Don't encrypt your files, don't have password protections, don't put printing restrictions on them. That makes it very difficult for us to use these documents when we receive them.

This one is a little bit less

intuitive, okay? We're going to talk about eSubmitter later, but if you're using a tool called eSubmitter to create your submission packages, if you open that package and modify it and then try and save it again, it will break the package such that it's unusable when we receive it, okay? You have to go back into eSubmitter, modify it there, repackage it, and export it and send it to us. We see that a lot, I wanted to make a point.

Okay, so acceptable file formats. Again, notice the icon. PDF, .docx, .txt files, XPT. These are SAS data files, we love those if anybody wants to submit them. Excel files, image files like JPEG and GIF. These are all acceptable file formats. The file name extension helps us identify the file type. So it's really helpful that you actually include the file extensions.

We do see documents within them, and that's not helpful. When you're naming your files, there are some things that you can help us

review and use these documents. Avoid special characters or foreign characters. Don't have really deep subfolders with really long names. We have character limits, and those are listed specifically in the technical specification. But if they go beyond that, we'll have to contact you and ask you to change them, because we can't use them.

Keep the path name under 180 characters, and if you are submitting data, if you're submitting tabular information, if you're submitting study information, you can use SAS for import files, XPTs for your data sets, including your analysis data sets.

Okay, eSubmitter. Has anyone used eSubmitter? Oh good, great. Yea, thank you. Keep going it. eSubmitter is a tool that we created to help people package their submissions. It's an FDA level tool, and when you sign in you go to this website. I have the entire link here so that you folks can see it, so you don't have to just click it and understand where it goes.

You can download the eSubmitter software.

So you're not using it through our website. What you're doing is downloading it locally, onto your own personal space that we cannot see or access, and creating a submission. So when you open it up, what you'll see is there's a number of templates, because this is shared by FDA. There are CRH templates, there are CDER templates. You want to choose the one that's relevant to CTP. So you'll see there is a CTP transmittal form up there. That's the one that you would choose.

When you're using it, you'll be walked through the process. It's fairly intuitive. It's a step by step guide, and then there's a way to attach all of the documents that you want to submit, right? Just attach them all in there and it creates a zip file.

The zip file can then be uploaded to the Portal, which we're going to talk about next. So there are a number of different resources for using eSubmitter. There's a user guide. There

are video tutorials. There's the checklist and technical working instructions, and if you get really stuck you can always email eSubmitter@fda.hhs.gov. So there's a lot of support for using this tool, and we find that helpful when we receive packages that were created in eSubmitter.

When you're done with eSubmitter, you can go to the CTP Portal to submit your CTP package. So who's used the CTP Portal?

(Show of hands.)

MS. ALLARD: Oh, okay. Awesome, great. We have some savvy folks here. So you can upload your eSubmitter submission files in the Portal. It also allows you to view your submission and administrative information. Here's the link to do it. Before you can use the Portal, you need to have an industry account manager created. We will talk about just some helpful tips for doing that in a few minutes.

So here's the welcome screen to the CTP Portal. You can see it has a number of

application types here. This is just dummy data that we've created. But you can see that, you know, you see a history of what you submitted under that account. And then you can go to the upload tool where it says, upload eSubmitter files. You are only allowed to upload eSubmitter files through the Portal, no other file types are allowed, and when you hit that button it just walks you through the upload process.

Okay. So in order to utilize the Portal, you have to request an industry account manager first. The industry account manager is someone that works for your company that has access to the account, but also manages the account. We don't manage that for you. What that means is you can give access to other users. You can create them, you can give them roles, you can delete them. That's all up to you, okay?

So in order to request this, you have to submit two signed forms. The first one is the cover letter and the cover letter needs to be signed by the authorized representative. The

second one is the rules of behavior. This one is signed by the person that they are designating to be the account manager, okay? So the authorized representative designates an account manager, and then the account manager can designate other people and create their user accounts within the Portal.

When it's completed in eSubmitter you can send it to us and we can usually create the IAM within 7 to 14 business days. You want to make sure that you leave that wait time prior to submitting your documents to CTP. Be sure that you request this account well in advance of submitting your application to CTP, so that you will have this available. If there are any questions or concerns about getting the IAM account created, this gives you a little bit of time to work back and forth. We have folks that you can contact, the eSub team, if you have any trouble.

So once we've received your request, we send you -- we email you a link, so you'll be

asked for your email address. You can click the link and create your first IAM account and then you can create other accounts for other people. If you don't click the link within 24 hours it's deactivated. That's an FDA policy, and then we'll have to create the link for you again, which is probably more annoying. So it's better to make sure that you're checking that email address on a regular basis after you use it. Okay.

So just some helpful tips, things that we've seen with this IAM request process. Most of it's fairly intuitive and most people get it fine the first time and we just move through smoothly. But just to be clear, the IAM form must be signed by the authorized representative who is a direct employee of the organization, okay? That's the person who can designate an IAM. We have to be careful about who we're giving these accounts to, right? You have to complete all fields legibly. Include the full legal name of the organization. Please don't

write self-employed, even if you're self-employed by an organization. Include the organization.

Include the full legal address of the organization. Don't include a personal address. We want the organization that you're requesting the account on behalf of. That's what we care about. Make sure the email address is correct. That's really important. That's how we'll communicate with you that your account's been created. So you'll want to make sure it's correct and then you'll want to monitor it pretty regularly.

Ensure that all the signatures are included on both forms. You need two. You need the authorized representative and you need the IAM-designated person to sign the rules of behavior. We do see forms with just one. Not everyone scrolls all the way to the bottom and finds that there's another signature required. So check for two first.

And then we need to use Adobe digital signatures with the date stamp, or we can use wet

ink for most. And if you need any help creating your IAM, the CTP eSubmission help desk is available for you to call or email.

Okay. So here's a handy list of resources. We have covered most of them, but if you come -- if you find that you are creating a submission package and you're not entirely sure where to go, you can do these. You can also always contact the CTP eSubmission help desk.

Okay. So does everybody have their phones handy still? We're going to go back to the Poll Everywhere quiz. Okay, you ready? You want to pull it up? Hey, look at that. A quick reminder, the poll is intended to be fun. I wanted to see where people were and I thought that we might have more participants on the webinar than we do in the room.

So we have someone in Russia, and the continent of Africa. That's really cool. All right ready? Next. Okay. In which module would a PMTA form be included? This is not a trick question, there may be more than one right

answer. Can you hit show responses? Hey, there's not a single incorrect answer.

(Laughter.)

MS. ALLARD: Spoke too soon. People found that clear response button quickly. Great. Nice work, yes. Module 1. Module 1 is our administrative information. This is where we would include all forms, and because we're FDA, we even made you use a form to order your box lunch today, which is amazing. All forms were modular. Okay. Next one.

All right. In which module would tobacco product manufacturing information be included? This is one is special for Todd. Yes. Todd's favorite module. Yes, Module 3, Manufacturing Information. Good stuff. I don't know if you were taking really nice pictures or paying really close attention, but we're off to a good start.

By the way, I want folks to know that I use this quiz to understand whether or not I'm communicating appropriately. It has more to do

with me and less to do with you, so if you are getting the questions wrong, I have not done my job and we'll all know it together.

Okay, next. Okay. Would an ENDS product and a cigar product be grouped into one submission? Again, that was really fast. I don't know if we only have one answer or -- that's 100 percent. But that was a resounding answer, yes. Okay. So it looks like everyone is familiar with their product information and their categories and the unique ID memo. That's great.

Next. What file types are included in an electronic submission to CTP? Again, not a trick question if you think there might be more than one answer. Oh, interesting. I'm glad this is happening. This is really helpful. Okay. So yes, PDFs absolutely. Excel files, yes, definitely include Excel files in your submissions to CTP.

Executable files. Please, no. I'm glad. Actually, I wonder if we'll see a change. Oh yep, people are clearing their answers. There

they go. Good, good. Get them down to zero. Our FDA OIMT folks won't allow us to receive executable files, because they run programs on our network that may or may not be harmful, okay? So if you have any questions about whether or not you should submit an executable file, please speak with your RHPM or call the eSub help desk, and we'd be happy to chat about it at length, trust me. Great.

Okay, next. How many signatures are included in the request for IAM account to use the Portal, one, two, three or four? Good. We're getting this right? And there's an overachiever at the bottom, but they've cleared it. Okay, correct. Two. Two forms, two signatures. Got it, good. Nice work.

All right next, and this is the last one. Again, this one's just for fun. I just want to make sure that people are enjoying themselves. Be honest. If you hated it, I promise I'll never do it again. It's important to know, yep. Maybe you don't care. That's

fine. Data. Data-driven decision-making.

(Laughter.)

MS. ALLARD: Oh yeah. I know who you are. Awesome, all right. That was our last question. Thank you guys. I really want to thank you for participating and having a little bit of fun with technology today. Thank you.

(Applause.)

MS. RADWAY: Thank you Ms. Allard. Okay, now we will start our first panel discussion, so can I ask the panelists to come up and take a seat? So as our panelists are coming up, just again a reminder to please introduce yourself and limit your initial remarks to no more than five minutes. Yes, Dr. Campbell, you can start.

DR. CAMPBELL: Hello. My name is Dr. Leanne Campbell. I lead the eSubmissions group in the Scientific and Regulatory Affairs Department at RAI Services Company. Our department is responsible for FDA submissions for Reynolds American Tobacco operating companies,

which include R.J. Reynolds Tobacco Company, American Snuff Company, Santa Fe Natural Tobacco Company and R.J. Reynolds Vapor Company.

My background is in biostatistics. I was part of the Clinical Studies Division at RAI for several years, leading up to my involvement in the Camel Snus MRTP. At last year's workshop on tobacco product application review, there was not a lot of granular, specific, information on how to compile a PMTA. We only had the PMTA guidance from 2016 and the public slide decks from CTP.

Also, the clock was ticking against various deadlines. But where there's a will there's a way, and we were able to use eCTD structure as a framework for formatting the PMTA files in a single directory. Since then, he proposed rule on premarket tobacco product applications and recordkeeping requirements was published in late September of this year, which contained details that may have provided clarity on some of our logistical unknowns. Earlier this

month, we submitted our first ENDS PMTA for the entire line of VUSE Solo products.

Now, we are learning that FDA has been developing an eTTD structure, which will be great for us to use going forward. Hopefully, this will mean we can streamline our applications against this common TOC for industry, which would remove some of the guesswork for industry on how CTP prefers these applications to be formatted.

The downside is that this standard TOC has not been provided until, I guess, today to us. So we were still operating under the previous assumptions on compiling a PMTA, particularly for those end market products that are bound by the May 2020 submission deadline. The small downside of this common TOC affects those of us in industry that submitted PMTAs before it was made available.

Combine that with the fact that only those PMTAs formatted in this standard format can be referenced in subsequent PMTAs, as per my understanding of reading the proposed rule for

recordkeeping, the proposed rule that was put out recently. In that case, if those early PMTA submissions containing bridging information across multiple product types, the sponsor would have to resubmit all of those bridging studies, either as a new PMTA or a TPMF.

The proposed rule clearly states that a sponsor cannot point to studies in a PMTA product on Product A from a PMTA Product B. So it seems like we would have no choice but to submit those bridging studies again to be reviewed a second time. We thought this was the opposite what CTP wanted us to do.

So why doesn't the sponsor just put all of those bridging studies in the TPMF? The answer is you can, but this is what you lose by doing so, hyperlinking. Collectively, the bridging studies have dual roles. One, to support the application, and two, to support bridging arguments from multiple platforms.

You wouldn't be able to hyperlink your source reports from the narrative if your

bridging studies in a TPMF. As a sponsor, a fully sourced hyperlinked PMTA is in our best interest. But if you're CTP and from the proposed rule, in hindsight this may not have been the preferred approach. And if I may harp on this for a moment, keep in mind that just a single clinical study can have 100 documents or more associated with it.

Our previous assumptions were that we were working in a flat folder environment. So we went with that assumption, and in case you haven't seen a PMTA in this format, it can be rather intimidating. Now if you've applied the eCTD structure to your application, then you as the architect would have no problem navigating this flat folder and finding exactly what you need. But to someone that wasn't privy to your thinking, it can be a lot more challenging.

I'll take this opportunity to pose this question. If we've already submitted a clinical study for VUSE Solo, do we need to submit that study again if it contains bridging

information on a different product? I'm hoping to gain clarity on why this rule was decided. The sponsors cannot refer back to PMTAs, the same way they can point to MRTPs or PMTAs on the same product.

Time permitting, I'm going to pivot to eSubmitter really quick. Support for XSL files was enabled this year, which is great. But we still need you to enable support for CSS files.

The packages we submitted for VUSE Solo contain CSS files, and although we were able to use a hack to allow eSubmitter to package these files, the packages that contain those files got stuck in the Portal, for lack of a better word, and had to be manually retrieved. If you have extremely large data sets, these can also get stuck and require manual retrieval at CTP.

Another issue is that once it's been sent through the Portal, there's no way to ensure that your submission has been received, other than the green checkmark. This is one reason why

we're advised to contact your RHPM in advance, to let them know you're planning a submission in case you should need assistance confirming receipt of your submission.

For VUSE Solo PMTA, as I mentioned some of our packages had gotten held up in their system, but the only way we found out was to contact the CTP help desk to understand what the issue was. All we can do is let CTP help desk know the number of files that were sent and compare that to the number that were received. I would add that the CTP help desk was very responsive during our submission.

In spite of the challenges I just outlined, the process of packaging in eSubmitter and submitting through the CTP Portal went fairly well. It just takes time. In fact, it would take less time to drive the submission to CTP than it took to package and submit it electronically. Sponsors should be prepared to allow for at least three days just for packaging and submitting through the Portal.

This concludes my remarks, and I look forward to the panel discussion.

MS. RADWAY: Thank you.

MS. MERSON: Hi. My name is Anuschka Merson, and I work for ITG Brands. I would like to thank you guys for the opportunity to participate on the public panel today. My experiences include submitting exemption requests, substantial equivalence reports, ingredients, and HPHC data.

While each company and submissions is different, one of the issues we've experienced internally includes making sure the operating systems are up to date to meet the requirements for packaging submissions and uploading. We have also found that the size of the file have delayed the packaging and uploading process. The FDA has updated their information on the website to help guide on file format size and specification for computer operating systems that should be used.

However, there was no notification that this information was updated. It would be

useful if when something is updated that it identifies it on the website so we can go and read and be more informed.

Additionally, there are certain processes and procedures regarding putting submission information together and uploading that exists in other industries that are very clear and easy to find on the website. However, it's not as easy to find the information the CTP website. One of the examples is a decision tree on which submission you need to submit to the FDA.

While the presentations that have been given have been very helpful, we feel that it would be helpful to have a webinar possibly giving some potential examples on what kind of submission and how the links, how we can potentially help you guys review the submission.

What has helped us the most is making sure we are prepared in uploading the submission and giving lots of time, being done way ahead of time and then doing the upload process, because

we always -- even if you're prepared, something always goes wrong and there's always time to send it in by mail. Thank you.

MS. RADWAY: Thank you.

MS. STARK: Hi. For those of you who do not know me, my name is Cristi Stark. I'm the director for the Division of Regulatory Project Management. I'm going to have some short remarks here so we have time to discuss. With respect to finding content on the website or figuring out what pathway may be appropriate, I'm going to use a plug for Call 1 of your assigned regulatory health project managers.

They can give you a decision tree over the phone or through email for you to make an appropriate choice. If you're not sure who your project manager is, you can always contact us through AskCTP and we can have somebody get back in touch with you. For the electronic, I'm going to push that off to Crystal.

MS. ALLARD: Hello. I think you all know who I am right by now, right? So if anyone

has ever checked my LinkedIn page, you will have seen that I have a professional motto that is directly relevant to what we're talking about today. It is, automate the mundane, so that you can focus on the interesting, okay? That is why we are asking folks to submit electronic submissions to FDA. It allows us to automate the process.

So I'm hearing that there are sometimes some difficulties in submitting and I'm glad that you're sharing that, because it allows me to go back and work on those and I will. That is my job and I like it, so I'm really -- I enjoy hearing this type of feedback because it knows me where -- it helps me know where I can help you to submit.

I don't like to hear that it's easier to drive that application to the FDA than it is to use the Portal. I promise to work on that, okay. In the meantime, I want you to -- I want to encourage you to think beyond just the submission but to the review process as well.

When we receive useful electronic information, we can use software to automate review process, to enhance and increase the efficiency of that review process.

It allows us to use our tools to pull information in, so that reviewers don't have to go hunting for it, and so that they can reuse it throughout their application. It's important that you think of a review team as a group of many people, many, many people, not just one person, and they're all looking at the same information.

We want them all to be looking at the same information in the same place, and we want to make it accessible to them with our tools. So that is why we are asking for folks to submit electronically. Thanks.

MS. RADWAY: Thank you, all right. So we did get a number of questions. So let's start with the first question and then maybe we can circle back to some of the points that our panelists made. The first one is, in the past,

the CTP website has frequently been updated with important information, marketing orders, scientific memorandums with no notice to industry. So is there a page where CTP might list those changes at the time, so that industry or other stakeholders know when those changes are made?

MS. STARK: So I'll start and see if Crystal wants to join in after. For the pages, there should be a date for last updated. In addition, I'm going to use this as a plug to encourage people to sign up for some of our notices through CTP. We actually have tweets, we have other types of outreach when there are important updates on the pages that people may end up missing.

I know when Ms. Redus went through her presentation today, she went through a myriad of slides at the end for who you could contact and how you could sign up for these updates. So I encourage you to look for those areas. Some of these emails blasts will actually alert

individuals so some of these updates.

The other plug is you can always call your project manager if you have a question, just to see if something has been updated.

MS. ALLARD: Yeah. You can also call the eSubmitter -- eSubmissions help desk, not the eSubmitter one. The eSubmissions help desk and see if anything new has been updated. Our website also has RSS feeds that you can sign up for that tell you -- they will send you an email notification when things are updated. So if you see a little icon up on the left of the web page that's an RSS feed, click it, put in your email address, it will email you.

Which reminds me, I also wanted to mention that the eTTD table of contents, the submission table of contents that I referenced today, was updated in the technical specification document that is posted in our website as an appendix, so it's there for you to reference.

MS. RADWAY: Crystal, this question is for you. Will there be -- will eTTD guidance be

available in time for industry submission deadline of May 2020? And I know we're not speaking to future guidance or regulation, but is there anything else, any other things coming up that industry can rely on as far as that is concerned?

MS. ALLARD: Yeah. So we're taking a baby steps approach to developing the eTTD. The creation of the Level 1 and 2 table of contents was the first baby step, and getting that published on the technical specification document was actually kind of a big deal for us, and not as easy as it may seem, based on how little information there is.

We are hoping to take more baby steps. The technical specification is not a guidance, right? That means it's a little bit easier for us to update incrementally. So I would say keep checking that pretty regularly, sign up for that RSS feed and keep apprised of that. That is currently our best way to share information about electronic submissions.

MS. RADWAY: Thank you. Okay, next question. The Portal contains a record of uploads and regulatory correspondence from FDA. However, the downloads like SE orders are not accessible. Can we expect this functionality in the future?

MS. ALLARD: Maybe. It's good to hear this feedback. If you find that useful, keep telling us and we'll look into whether or not we could increase the functionality within the CTP Portal. I will tell you that in the Division of Regulatory Science Informatics, we are taking a close look at all of the tools and technology that we're using, and looking toward the future, and the Portal won't be excluded, okay?

MS. RADWAY: Okay. Next question, is it possible for further work to be done with respect to the availability of electronic submitters to hide their personal information from public review, such as their name? And then, how can that be done?

MS. STARK: I'll start, and maybe you

guys want to join in as well with some of your experience. When it comes to what is being placed out in the public domain, we have to follow set regulations and statutes regarding protection of trade secret, personal privacy, or commercial confidential information.

Names are not under that grouping. So this is why you will see some of the names out there when it is posted, and that's the simple response for it. I'm not sure if you have anything to add or maybe the two of you, with your experience submitting electronically, if that's been an issue.

MS. ALLARD: I don't -- that's not an electronic problem, so much.

MS. MERSON: No. We've had no issues. I don't -- but we are always --

MS. RADWAY: Can you speak closer to the mic?

MS. MERSON: But your name is associated with it, but I don't think we've had any issues with that.

DR. CAMPBELL: No issues here either.

MS. RADWAY: So one thing I wanted to come back around to was Dr. Campbell talked about cross-referencing PMTA studies from other PMTA submissions. Cris, Ms. Stark or Ms. Allard, do you have any comments on that?

MS. STARK: Okay. So we'll just be completely transparent here, and Dr. Campbell was very kind in her remarks as well. We have been growing over time since the Center first started, and we first started with complete paper submissions. We moved to electronic submissions in physical format that were driven by a courier, which we would like to get to electronic submissions, so we're no longer driving our submissions here. It's green and it's just easier for all.

With respect to the idea for cross-referencing, baby steps again here. So and I'll just, I'll be honest with it. We are here to take feedback, see what's going on. Right now, if you're looking at submission of an application

for a PMTA, we are asking for that submission to really be a nice stand-alone with the exception of cross-referencing to Tobacco Product Master Files, which you'll hear in a presentation later today from Ms. Amyot.

We have not yet gotten to the point for cross-referencing one study in the PMTA to another, and as you can see in the proposed rule, which we'll discuss with some later presentations today as well, we're really looking at that PMTA when we're talking about that group submission to stand when we're looking here, rather than having a submission reference back to something from four years ago.

You asked a question about a current application that you submitted in for VUSE Solo, referencing it to other products. We are happy to look at the idea for where we can go with electronic submission. This is something that we need to work on internally and maybe update technical specifications if we have some items there or a potential workshop or other items that

may be helpful in the future.

Right now what we're looking at is the idea of a submission that is grouped, where you have your information in there that we can go across that same product category or subcategory, and the use of a Tobacco Product Master File. Right now, that's where we're at. It may be very different in a year or so.

MS. ALLARD: Yeah, that's a great intro. So I think the idea in the proposed rule is a bit reactionary to the fact that we've been receiving non-standard paper semi-electronic submissions for so long that we feel the need to make sure that we have all of the information that we can do to do a review in one cycle, right?

Looking toward the future and coming back to the idea of taking baby steps, we do really want to work toward a fully electronic submission, which would allow us to think differently, right? We wouldn't have to think in terms of, what do we do if we can't find the

information? We'd be able to reliably expect that we can find the information we're looking for, or that it's not there, right? Not that we've missed something.

This is what keeps reviewers up at night, like what if I missed something and I made a horrible decision? We're trying to help them make the best decisions that they possibly can by giving them the information they need to do that, and electronic submissions help them to do that. We are going to continue to work on making sure that we create standard submissions that you can use, and we are going to continue to communicate those in whatever ways we possibly can.

I loved the plug for the webinar. I didn't even have to say it, but that's a great idea. We will take that, yes. If you will come and promise to continue to participate, because you know I like that, we will continue to try to share information as each baby step is taken and available for you.

MS. RADWAY: Are there --

DR. CAMPBELL: I had a -- I think that's actually really encouraging to hear that, you know, the basis of that statement in the proposed rule was really more so about paper submissions and not so much about electronic submissions. Hopefully there's a middle ground we can get to so these don't have to be reviewed more than once.

MS. STARK: With that, please submit your comments for that so it can be addressed during the rulemaking process. I encourage everybody, please submit your comments. It is currently open.

MS. ALLARD: Yeah. The more we build an argument for electronic submissions, the easier our job is to communicate to you that we want them and how we want them.

MS. RADWAY: Is there anything else we want to add about receiving confirmation of those submissions?

MS. ALLARD: Yeah. So right now you get the green checkmark in the Portal. The other

way to know whether or not your submission has been received at the DCC are the automated acknowledgments that come through the Portal, that are really generated by the gateway that we use as part of our Portal.

So there are these like auto-created acknowledgment notifications that are not letters, but are another source of information that your documents have been received. And again, as we're looking to update the Portal, knowing what would be helpful to you is helpful to us, and we can continue to work on ensuring that you have the type of communication that you need to feel comfortable that your submission was received.

MS. STARK: I'm going to add to that a little bit as well. The automated acknowledgments that you're receiving is just showing that content is being received across our gateway at our Document Control Center. We're going to be looking and working with industry to make sure that we're getting all pieces. That

acceptance letter is really what is key so we know when we have a complete application and the dates for submission and receipt.

We're going to ask for your help if there are issues with not being able to identify when things have been submitted and received, or other types of errors. Please bring them to our attention through either the eSub help desk or through your regulatory health project managers, that we can continue to work on it and improve.

MS. RADWAY: Thank you. Okay. We have an additional question. This says, Crystal's slide suggests that only three literature research review searches, non-clinical, clinical, and population health. Does that mean a single all-encompassing literature review is not acceptable? And then a second part to this question, where should we put literature reviews for toxicology, human health risks and human factors?

And I want to just say this question might be better suited for a later presentation.

So I'm going to hold this one for later today. You guys don't need to answer that one. Next one is, what are the major challenges of referencing the other parts of submissions? I wanted to see if one of our industry reps could speak to that. For referencing other parts of the PMTAs.

So with -- you spoke to cross-referencing other studies in the PMTAs. So can you talk more about, like, what the major challenge is with that?

DR. CAMPBELL: In a future PMTA on a Product B let's say. Let's say VUSE Solo is Product A and then the next submission is Product B. So we have a number of clinical studies that resulted from some of the original timing that was put around the deeming rule and when we had to have our applications put in.

So we had to get creative and combine products in a single study. So we've already submitted some, a lot of them for VUSE Solo, and the challenge is how do we reference that same study from a PMTA if we're not allowed to point

to a PMTA? But if we can point to a PMTA, then it seems like it would be something similar to pointing back to a MRTP. Just reference it by the number and explain where it's located in the application.

This is what I thought, without any other information, how it would work. Maybe we're not as far away from that as I thought, but it would seem advantageous to everyone not to review a study more than once.

MS. STARK: So some of it I can agree with. With some of it, there may be a difference in how you review a study based on the context for that particular application, which is why we've been a little bit careful with our cross-references. You bring up a great example of looking at a cross-reference for a single study between a PMTA and a MRTPA.

We have had cases with current applications that are out there in the public domain, such as a recent one that was authorized, where we did have that back and forth, where we

knew it was for these same products with the same study being used in a similar context. We still must look at it for the different review standard.

There is a difference between a PMTA or an MRTPA. There also may be a difference if you're looking at a particular study for a PMTA for one category or a subcategory versus another. So part of it, when we're in our review processes here, is going to be the context.

MS. ALLARD: I'm going to address the literature review question, sort of. It is not my job to tell you what to submit to CTP. There will be later presentations who will cover that in-depth. That's their job and I'll let them cover it. But the eTTD table of contents is created to be the same for all submission types to CTP.

So it's important to understand that if a section of that table of contents is irrelevant to the submission that you are submitting, you're not expected to necessarily

put documents in every single section. You're expected to look through all of the information that you want to submit as part of a submission, and then take that and put it in the appropriate section.

And if there is an empty section, don't submit anything including the folder, like nothing. Just leave that section blank. Leave it out, okay? So the eTTD is not where you go to figure out what you should be submitting as part of a submission. Those are for other rules and guidances and policy. The eTTD just tells you where to put what you're already planning to submit.

MS. RADWAY: Okay, thank you. Next question, and I am going to assume this is going to be directed towards Ms. Stark. When and how do you get assigned a project manager?

MS. STARK: Project managers are actually assigned by company. We typically assign a project manager when we receive a submission in. So one of the common things that

we talked about today with electronic submissions is you need to have an industry account manager assigned, in order to submit across.

We do not give you a project manager when you are being assigned an IAM, because the IAM is not truly a submission. It's just a way to submit your applications into us. If you send a PMTA across, you will be assigned a project manager. You will receive a letter. At the bottom of the letter, and you're going to see in a later presentation what it looks like, you will have the name, the phone number, and the email address for that project manager assigned.

In addition, I encourage you to pay attention to your letters, because occasionally we do have staff leave or we have staff get promoted or rotate, so your project manager could change. I will also note, if you are not sure who your project manager is, you can always go through the AskCTP or our help desk and we can try to get an appropriate answer for you.

MS. RADWAY: Okay, thank you. I guess

I just wanted to take this time, since we have a little bit of extra time, to find out if there's something on the website or something presented today that either of our industry representatives think would be stand out or helpful for someone new going to the website, or someone new getting ready to submit a new application?

DR. CAMPBELL: I really do think the eTTD structure is going to be super-helpful for most people. We're already on a path. I don't know how well we can merge our methodology into eTTD at this point in time, given the May 2020 submission deadline. But I feel like it's definitely worth considering and actually using if we can do that.

So for someone just now entering the field, I think the fact that that exists now is huge. It's very, very important and very helpful.

MS. STARK: Do you mind clarifying a little bit why it would be difficult to shift now to this format, by the May 2020 deadline?

DR. CAMPBELL: That's because a year ago or so, or maybe two years ago, we were under the assumption that we would be submitting these applications in a flat folder environment and single directory. So we built all of our processes around that notion, and now we have a sort of template for future PMTAs by having submitted VUSE Solo PMTA already in a single directory, in a flat folder environment.

So it would just take some planning and thinking about how we can convert from that into an eTTD. I totally think it can be done. I'm not sure we have the time.

MS. STARK: And that's for PMTAs. What about for SE reports or exemption requests?

DR. CAMPBELL: I wasn't aware that the eTTD was expected to be used for SEs or exemption requests, but since that is the case, I think the colleagues that I know could make use of that easily.

MS. MERSON: I think we can use those, but even knowing this information up front before

even the SE or PMTA guidance documents is very useful in planning, because this is kind of the first step on how you set everything up before you -- well, before you gather all your information. So I think for the SE and exemption requests, there's definitely still more time. They're obviously smaller from the PMTA submissions.

MS. RADWAY: Are there any additional remarks or questions?

MS. STARK: I was actually hoping that both of you could share your perspective for important lessons learned with the electronic submissions currently, and then maybe just what you're thinking of based off of the presentations this morning for where to go and maybe time lines towards May 2020 for others that haven't embarked on this yet?

MS. RADWAY: Thank you.

MS. MERSON: I think understanding and going on FDA website and reading the file size and everything in order to make your submission

successful is key. We have spent -- we've been up since 3:00 a.m. because the files were too big. So making sure you split them out is very important. Go and read all the information that is on FDA website and ask questions way in advance.

MS. STARK: So I'll give one last plug. I know that May 2020 is coming up and people are very nervous. But I'm going to ask that you don't wait. If you know that you need to create an account and get an industry account manager, do it now. Although it only takes 7 to 14 days to have that in place, that is when everything is filled out and appropriate.

We have had cases where we have to go back multiple times. I also want to make sure that people are submitting their applications earlier rather than at 11:59 p.m. on May 20th, when they're due. The biggest issue I'm looking at is if there is some sort of snafu or issue, you may miss the deadline.

So I'm going to ask that you guys plan

for it early, utilize our help desk and our resources here if there are questions, and are we willing to look at maybe test -- testing, test submissions?

MS. ALLARD: Yeah, yeah. So if you're interested and prepared and an early planner, you can submit a test application to CTP. You would get in contact with our eSubmissions help desk first and tell them that you'd like to submit a test submission.

You can package it up and send it to us and we'll tell you if we found any technical issues or technical deficiencies within that package, and then you can feel more secure that your package is ready to be submitted. That can be done any time. You don't have to wait.

MS. RADWAY: So just to confirm Ms. Allard, that's the CTP eSubmissions help desk, right?

MS. ALLARD: Yes, the CTP eSubmissions help desk. The information for that is on our manufacturing web page. If you scroll all the

way down to the bottom, you'll find information about electronic submissions. Maybe someday we'll get our own page specific to electronic submissions with more information, so keep your eyes peeled.

MS. RADWAY: Okay. Well, I want to thank all our panelists for joining us for this first session. We're now going to take a break for 15 minutes, so we will be back at 10:37. Thank you.

(Applause.)

(Whereupon, the above-entitled matter went off the record at 10:22 a.m. and resumed at 10:40 a.m.)

MS. RADWAY: So now we're going to start Session 2, Pre-Market Tobacco Product Applications, Review Process, and Resources. First up we have Ms. Emily Busta to talk about the review process of PMTAs, and then Ms. Sarah Amyot to talk about Tobacco Product Master Files.

MS. BUSTA: Okay. Good morning, and thank you again for your participation in this

meeting. My name is Emily Busta, and I'm a regulatory health project manager with CTP's Office of Science. This morning I will be speaking about premarket tobacco product applications, otherwise known as PMTAs.

In this presentation, I will begin by providing an introduction to the three pathways available to market a new tobacco product, and I'll go into more detail in PMTA specifically. First, I will describe the statutory requirements and the review phases for the PMTA. Then I will go through a discussion of some recent metrics and key features, and finally I'll wrap up with the variety of resources that CTP has made available to applicants.

Let's begin with an introduction to the marketing pathways available to market a new tobacco product. There are three pathways available to bring a new tobacco product to market in the United States, premarket tobacco product applications, or PMTAs, substantially equivalent reports, or SE, reports and requests

for exemption from substantial equivalents, or EX requests. This presentation will focus on PMTAs, while later presentations will discuss in detail SE reports and EX requests.

To introduce the PMTA pathway, I will begin with the statutory requirements as described in Section 910 of the Federal Food, Drug, and Cosmetic Act. An order under Section 910(a)(2) is required to legally introduce and market a new tobacco product in the United States. The PMTA pathway has been considered the primary pathway for a new tobacco product to come to market.

This is based on Section 910, which requires authorization for new tobacco products through a 910(b) application. However, other pathways such as SE reports and EX requests may be more applicable for some. These pathways are also provided for in the statute as an alternative to the PMTA pathway. While many, many manufacturers have primarily utilized SE reports, there are cases where a PMTA is more

appropriate.

For example, the PMTA pathway could be used for new tobacco products that do not have a valid predicate product for comparison. Please note, that a new tobacco product that receives a marketing order by the PMTA pathway cannot be used as a predicate for an SE report. You will hear more about the SE pathway in another presentation.

At this time, FDA intends to limit enforcement of the requirements of Section 910 to finished tobacco products, including components and parts of deemed products sold or distributed separately for consumer use. FDA does not at this time intend to enforce these requirements for components and parts of deemed products that are sold or distributed solely for further manufacturing into finished tobacco products, and not sold separately to the consumer.

For a PMTA, CTP review is looking at whether marketing of the tobacco product for which an application has been submitted meets

four main criteria. First is whether the product is appropriate for the protection of public health. This is determined with respect to the risks and benefits to the population as a whole, including users and non-users of the tobacco product.

This consideration also takes into account the increased and decreased likelihood that existing users of tobacco products will stop using tobacco products, and the increased or decreased likelihood that those who do not use tobacco products will start using tobacco products.

Applicants may consider vulnerable populations that are disproportionately impacted by tobacco product use. Some examples of vulnerable populations include adolescents, those that are socioeconomically disadvantaged, racial or ethnic minorities, under-served rural populations, pregnant women or women of reproductive age, and sexual or gender minorities.

Additionally, CTP review will look at an application's conformance to the requirements of Section 906(e), which deals with manufacturing processes, the proposed labeling, which should not be false or misleading, as this may render the product misbranded under Section 903, and that the product conforms to any product standards under Section 907 which apply, or it must contain adequate justifications for such deviations.

Now that we have discussed the statutory requirements of the PMTA pathway, I will go through the review phases. The PMTA review process is divided into distinct phases. The chevron diagram shown on this slide is representative of the phases. However, please note this is not drawn to indicate the time required for each phase of the review.

Phase 0 or the pre-submission meeting is not a required phase, but may be requested by an applicant to discuss pertinent end points. Phase 1 is the acceptance review phase. Phase 2

is the filing review phase. Phase 3 is substantive review and action phase, and Phase 4 is the post-market reporting phase.

As described in Section 910(c)(1)(A), the PMTA pathway has a 180-day review period. To determine when the 180-day review period begins, FDA generally relies on the date of receipt of a complete application by CTP's Document Control Center. Or, if samples are the last part of an application submitted, the date at which samples are received.

I will now describe each phase of the review process in more detail. Phase 0 of the submission review process is the pre-submission meeting between the applicant and CTP Office of Science. It is considered Phase 0 as this is not required for PMTA submission. However, CTP encourages applicants to request appropriate meetings, as we find that after meeting with CTP an applicant may have a more robust knowledge of what ought to be included in their submission.

In general, meetings should be held at

least a year in advance of a planned premarket submission. This allows the applicant the opportunity to consider, account for, and implement, any changes that may result from CTP feedback prior to preparing their full application. This may include, but it is not limited to appropriate samples, inspections, discussion on clinical end points and any other clarifying questions.

Please note the FDA is not a consultant. It is up to the applicant to make the case for the studies they're conducting and the data they are submitting. There are many useful, publicly available resources on CTP's website to aid an applicant in the preparation of a PMTA. This includes webinars, memos and guidance documents. Links to many of these will be provided at the end of my presentation.

If you would like to request a meeting, CTP has issued revised guidance in July of 2016 on meetings with industry and investigators on the research and development of

tobacco products, which provides further information on how to plan requests, and what to expect from meetings with the Office of Science.

Phase 1 in the review process is the acceptance phase. During the acceptance phase, CTP will review an application to ensure the product falls under our jurisdiction. If it falls under CTP jurisdiction, a regulatory health project manager completes a high level preliminary review to determine if the application on its face contains the statutory requirements applicable to PMTAs, or they refuse to accept procedures for premarket tobacco product submissions, or RTA rule, which will be discussed next.

The RTA is applicable to all tobacco product applications, PMTAs, modified risk tobacco product applications, or MRTPAs, SE reports, and EX requests. FDA may refuse to accept an application if any of the ten criteria listed in this table apply.

In the first column of this table, we

discuss the format of the application, which should include that the application is legible. An application may not be legible if, for example, it includes documents which did not transfer completely or have low resolution. The application is to be provided in the English language. If any portion of the application is submitted in a foreign language, it should also include an English translation. If submitted electronically, the application should be in a format that CTP can process, read, review and archive.

Electronic formats include submission through CTP Portal, the electronic submission gateway, and physical media such as CDs, DVDs, or hard drives. You may refer to the FDA website for additional information on electronic submission file formats and specifications.

A submission should also include the applicant name and contact information, and the full product identification. This information includes the product manufacturer, category and

subcategory, the product name, package type, package quantity, and characterizing flavor. I will discuss the full identification of tobacco products in a bit more detail in the following slides.

The RTA rule additionally requires that if the submission is received from a foreign applicant, an authorized U.S. agent that resides in the U.S., or has a place of business in the U.S., must be identified within the application, along with their contact information.

Number 7 in this table is in regards to the submission containing FDA required forms. Currently, there are no required forms for PMTAs. The type of submission should be provided by the applicant. If requesting PMTA, SE, EX, or MRTPA, this should be clearly identified in the application. The submission must contain the signature of a responsible official. A responsible official is a person authorized to make decisions and act on the application.

For all submission types, excluding abbreviated reports, the rule states the submission must include a valid claim of categorical exclusion, or an environmental assessment. At this time, there are no categorical exclusions in place for PMTAs. Therefore, an environmental assessment must be submitted as part of a PMTA.

I would like to spend some time on the full identification of a tobacco product as a requirement of the RTA rule. Full ID includes the following criteria: the name of the manufacturer of the new product, product name, category, subcategory, package type, package quantity and characterizing flavor. Providing this information in an easy to find and readable table is useful to assess the regulatory health project manager in performing an initial review.

On the following slides, I will provide a couple of examples of full and unique ID tables for some ENDS products. On this slide, you will see an example of full and unique ID for

a closed e-liquid. Full ID is required for acceptance, but unique ID is necessary as we move through the review process. In addition to the properties required for acceptance, seen in this table in blue, there are additional product properties that are useful for uniquely identifying tobacco products.

Some of these additional properties for an e-liquid can be found in red on the table. These may include, for example, e-liquid volume, nicotine concentration, the ratio of propylene glycol to vegetable glycerine, and additional properties as necessary. Additional properties will be added when the list of properties are not sufficient to identify a tobacco product. Additional properties necessary upon identification may not be identified during acceptance phase, but may be found during substantive review.

Your PMTA can be a group submission including more than one related product. However, you will need to provide full ID for

each product. For example, if your submission includes an e-liquid as identified in this slide and an open e-cigarette, full ID will need to be provided for each of these ENDS products. On the next slide, I'll provide an example of identification for an open e-cigarette.

Here you can see one example of product identification for an open e-cigarette. Please note this is just intended to serve as an example, and assigned product properties will be determined on a case by case basis. For an open e-cigarette submitted as an independent PMTA or grouped with other ENDS products, the same criteria is required for full identification in order to meet the acceptance criteria.

Again, these are shown as blue text in the table and include product name, category, subcategory, package type, package quantity and characterizing flavor. Unique ID may also be provided. You can see some additional properties for unique ID in red text in this table.

The premarket tobacco product

applications for electronic nicotine delivery systems guidance for industry provides lists of product properties that FDA recommends and unique identification of ENDS products. A PMTA must be submitted for each version of a tobacco product. Any change to the tobacco product properties constitutes a new product requiring its own PMTA. This may include, for example, changes in flavor, battery capacity or others.

At the end of Phase 1, CTP will issue one of two types of correspondence. If the application is missing a required element, the applicant will receive a refuse to accept letter, which will include the reason for refusal. If refused, the applicant can submit a new application once they are able to provide all of the statutory and regulatory requirements.

If the application appears to contain all of the required elements, CTP will issue an acceptance letter, which will inform the applicant of their submission tracking number, also known as an STN, and will include the

contact information for the regulatory health project manager assigned to their application.

The RHPM will be your main point of contact for any issues related to your application. They are the people that you should contact should you have any questions throughout the process. If the application is accepted by CTP, it moves to the next phase, filing review. As outlined in Section 910(b)(1), the purpose of the filing review is to determine if the application contains information to initiate substantive review.

During filing, CTP will conduct a more in-depth, multi-disciplinary review of the data as submitted, to determine if all statutory and regulatory requirements have been provided, as outlined in Section 910(b), Parts A through G, which are discussed on this and the following slide. Regulatory and scientific reviewers will determine if the application includes full reports of all information published or known to, or which should reasonably be known to the

applicant regarding the health risks of tobacco products, and whether the tobacco product presents less risk than other tobacco products.

This information should include, for example, comprehensive study results, case reports, complete data sets and analyses, as well as the analytic code used to analyze the results. Additional detail on the scientific contents to be included in a PMTA will also be discussed in a subsequent presentation. Applications should include a full statement of the components, ingredients, additives and properties and of the principle or principles of operation of the tobacco product.

For example, here a toxicology reviewer may look at the ingredients of the product to see if there is enough information to permit substantive review for their respective discipline. A full description of the methods used and the facilities and controls used for the manufacturer, processing and when relevant packaging and installation of the tobacco product

should also be included.

For example, an application should contain the addresses of the applicant's manufacturing facilities, process flows, descriptions of steps in the manufacturing process and others. PMTAs should also include an identifying reference to any tobacco product standard under Section 907 that applies, samples of the tobacco product and components thereof as reasonably may be required.

Samples allow for FDA to independently test the product that is the subject of the application. In general, a PMTA is considered incomplete until FDA confirms receipt of at least one sample of the proposed tobacco product. Generally, the number of samples CTP requires for testing will be identified in a separate sample request letter. If samples are not received, this may result in refusal to file.

Specimens of the proposed labeling to be used for the tobacco product should be included in the submission, as well as any other

information relevant to the subject matter of the application. Other information may be identified during the pre-submission meeting if held, that is specific to the tobacco product.

At the end of the filing phase, similar to the acceptance phase, CTP will issue one of two types of correspondence. If the submitted information is inadequate to continue with substantive review, the applicant will receive a refusal to file letter. In this letter, FDA will include the reasons for the refusal. If refused, the applicant has the option to submit a new application once they are able to meet the filing requirements for a PMTA.

If the application meets the filing requirements for a PMTA seeking a marketing order, CTP will issue a letter to notify the applicant that the application has been filed. If filed by CTP, the PMTA moves into Phase 3, which deals with substantive review and results in an action by CTP.

The substantive review phase is a

multi-disciplinary approach to review the data submitted by the applicant and determine if such data is sufficient to demonstrate that authorizing the marketing of the new product would be appropriate for the protection of public health.

During the substantive review phase, CTP's Office of Science, in conjunction with the Office of Compliance and Enforcement, may conduct inspections of clinical or manufacturing facilities. You will hear more about inspections in a later presentation.

Additionally, CTP may conduct testing of the new product. At this phase, CTP should have received the samples requested in the sample request letter. An application may be referred to the Tobacco Products Scientific Advisory Committee, also known as TPSAC. If the applicant would like CTP to consider referral to TPSAC, they should include this request in the cover letter of their initial submission. Along this request, it would be helpful for the applicant to

provide a reason as to why TPSAC referral is being requested.

CTP has the discretion to refer a product under consideration to TPSAC, and will determine this during the substantive review phase.

CTP generally expects that when an applicant submits a PMTA, the submission will include all information required by Section 910(b)(1) of the FD&C Act. However, CTP recognizes that additional information may be needed to complete the review of a PMTA. If CTP determines additional information is needed to render a decision, the applicant will be notified by letter and given a period of time by which they will need to respond.

During this time, review of the application is suspended and the clock is stopped. If CTP receives an amendment to a PMTA that contains a substantial amount of new data that has not been previously submitted or reviewed by CTP, such as new data from a

previously unreported study or detailed new analyses of previously submitted study data, where it requires additional CTP review time, this amendment will be considered a major amendment, and CTP will consider the submission of this information as if you have submitted a new PMTA.

Because Section 910(c)(1) of the FD&C Act requires FDA to issue an order for an application meeting the requirements of Section 910(b)(1) within 180 days of its receipt, a new 180 day period will begin upon the receipt of a major amendment. CTP generally does not intend to review unsolicited amendments that would require significant review time by the agency. If the applicant submits information that is not requested by CTP, this may be identified as an unsolicited amendment and CTP is not obligated to review the submission.

The review and action phase may result in the issuance of four letter types. A deficiency letter, environmental information

request letter, a marketing granted order letter or a marketing denial order letter. If CTP completes review of a submitted PMTA and determines that scientifically the new tobacco product is appropriate for the protection of public health, but review of the environmental assessment determines that additional information is necessary for us to determine whether to prepare an environmental impact statement or finding of no significant impact, an environmental information request letter may be issued.

In response to the environmental information request letter, the applicant can submit an amendment to address the identified issues. Additional details on the environmental assessment and its contents will be discussed in a later presentation.

After the completion of the review phase, FDA will determine if marketing of the product under review is appropriate for the protection of public health, and if it may be

introduced or delivered for introduction into interstate commerce. In general, within 180 days an applicant will receive either a marketing granted order or a marketing denial order.

A marketing determination will be made on each specific product, not the submission. If an application is denied, a rationale for the decision will be provided in the issued letter. If denied, the applicant will have the opportunity to resubmit their application. If authorized, the applicant will be provided a marketing order letter, notifying them that the new tobacco product is appropriate for the protection of public health and you have met the other requirements of Section 910(c) of the FD&C Act.

Under the provisions of Section 910, you may introduce or deliver for introduction into interstate commerce the new tobacco product. If there are any restrictions on the sales and distributions, these will be described in the marketing order letter. If after review of the

submission marketing orders are authorized, CTP will generally request any post-market reporting needs in the marketing order letter.

These will vary based on the product and the submitted data. However, examples may include serious or unexpected adverse experience reporting, which we request within 15 days after the report is received by you, any manufacturing deviations and other reports such as annual or biannual reports, or updates to ongoing studies. Again, the marketing order letter will detail any specific reports and time lines for these reports.

Post-market reporting is led by CTP's Office of Compliance and Enforcement, not the Office of Science. Your order letter will provide the contact information for your OCE point of contact.

Now that we have had an opportunity to discuss the statutory requirements of the review process, I will describe some metrics the last fiscal year, reiterate some key features of the

PMTA pathway, and wrap up with some helpful resources CTP has made available.

But first, a note about withdrawals. Applicants are allowed to withdraw their PMTA for any reason at any time in the process prior to a marketing determination by CTP. To withdraw an application, an applicant must submit a request to CTP in writing. Upon receipt, we will issue a letter acknowledging this withdrawal request, thus ending the review of the product.

If the applicant would like to submit the same product for review, all information must be resubmitted in a new PMTA. In your resubmission, you may not cross-reference to a closed application. That is one that has been previously withdrawn, received refuse to file or received a refuse to accept.

To capture CTP's experience with review of PMTAs, I will now discuss some metrics. The metrics presented will be broken out into statutorily regulated products such as cigarettes, roll your own and smokeless tobacco

products and deemed products, for example cigars, water pipes, pipes and ENDS. I'll present on both fiscal year 2019 and cumulative metrics.

Please note that the numbers presented today are subject to change as they only reflect application status through September 30th, 2019. On this slide, I am showing some recent metrics related to the PMTA program for statutorily regulated products for fiscal year 2019. For clarity, fiscal year 2019 runs from October 1st, 2018 to September 30th, 2019.

By the close of the 2019 fiscal year, we had received four PMTAs, two of which are open, meaning they are within the FDA review process, and two of which are closed. In the table on this slide, you will see some of the most common types of closed actions.

On this slide, I'm showing cumulative metrics related to the PMTA program for statutorily regulated products. For clarity, cumulative metrics include all PMTAs received to date, from the start of the summer through

September 30th, 2019.

As of September 30th of this year, CTP has received 29 PMTAs for statutorily regulated products. Of those 29, 21 have been closed and eight are still open within the FDA review process.

Now I'd like to shift our focus to deemed tobacco products, as this is one of the main points of this meeting. On this and the following slide are some recent metrics for deemed tobacco products in the PMTA pathway. We have received 16 PMTAs for deemed products in the 2019 fiscal year. Of those 16, 15 are still open in the review process with FDA and one is closed.

This slide captures cumulative metrics for PMTAs received for deemed products. CTP has received 389 PMTAs for deemed tobacco products. Many of these were received prior to fiscal year 2019. Of these 389, 370 were closed. A large number of these were closed due to a lack of environmental assessment. It is important when submitting an application that it contains all

required elements.

As discussed earlier in my presentation, there are no categorical exclusions in place for PMTAs. Therefore, an environmental assessment is required. A lack of environmental assessment will result in a refusal to accept. As you can see, there are 19 open PMTAs for deemed products within the FDA review process.

We would like to highlight key features of the PMTA pathway that makes it unique to other pathways. The PMTA pathway is the primary way to legally market a new tobacco product. This is because, as previously stated, a PMTA does not require a predicate tobacco product to compare to, as is required for SE reports.

A PMTA is for a new product that is not equivalent to a product already on the market, and to be authorized the new product must be found appropriate for the protection of public health. This may include comparisons to other

tobacco products in the same category or in other categories or subcategories. You will hear more about the scientific standards in later presentations.

Also, new tobacco products authorized by a PMTA are not eligible predicates for SE reports, but they may be used as original tobacco products for EX requests if the tobacco products are modified by the addition or deletion of a tobacco additive or increase or decrease in quantity of an existing additive.

A PMTA may require post-market reporting, which will be communicated in the marketing order letter. Please be sure to read this letter thoroughly, as it will outline important information. A PMTA may be referred to TPSAC; however, it is not required, and samples may be required to facilitate CTP testing and verification of certain characteristics of the new tobacco product.

Generally, action on a PMTA will occur within a 180 days of receipt of a complete

submission. As you may be aware, on September 25th, 2019, FDA issued a proposed rule to set forth requirements related to the content, format and review procedures for PMTAs as part of the agency's continued commitment to its oversight of e-cigarettes and other tobacco products.

When finalized, this proposed rule will help to ensure that PMTAs contain sufficient information for evaluation such as details regarding the physical aspects of the tobacco product and information on the product's potential public health benefits and harms.

It also would codify the procedures by which the agency would review PMTAs and establish requirements for manufacturers to maintain records related to the legal marketing status of their tobacco products. The proposed rule is intended to provide both applicants and FDA with more certainty related to the information needed to demonstrate FDA's review processes, with the goal of an efficient and predictable review process.

For example, the proposed rule will establish a requirement for the electronic submission of PMTAs, address the 180 day review period and describe when FDA may pause or extend the review clock, describe how applicants may use scientific literature, or bridge the results of an existing study conducted using a different tobacco product to demonstrate health risks of its own product, explain FDA communications with applicants, including when FDA would issue deficiency letters, and identify post-market reporting requirements for tobacco products that receive orders to ensure FDA can sufficiently monitor the marketing, use and impact of such products.

Per the rulemaking process, once the comment period for the proposed rule closes, currently set to 60 days closing on November 25th, 2019, FDA will review and analyze the comments and then determine the appropriate next steps. CTP is inviting comments on the topic in this proposed rule and we want to hear from you.

Please read the proposed rule and submit your comments before the window closes.

In closing, please find a few key take-home points on the PMTA review process presented here. When submitting a PMTA, there is the opportunity for applicants to submit group submissions. This means that if you plan to prepare an application for a number of similar products, you can submit one application, so long as it identifies the full product ID for each product as this will facilitate review.

CTP generally will make a determination on the number of unique products and assign STNs to each product as appropriate. For group submissions, an applicant can also utilize the Tobacco Product Master File if appropriate, which you will hear more about later this morning. Applications must contain all required elements for filing.

Submitting a piecemeal submission may impact a filing determination. For example, if a PMTA is submitted with a preliminary report of a

clinical study without full data sets or analyses, this may impact the filing determination. If CTP determines additional information is needed to render a decision, the applicant will be notified by letter and given a period of time by which they will need to respond. FDA is not obligated to review unsolicited amendments.

In general, within 180 days an applicant will receive either a marketing granted order or a marketing denial order. A marketing determination will be made on each specific product, not the submission. Finally, please go to FDA's website and take the time to read and review the proposed rule. It is currently open for public comment until November 25th, and we look forward to receiving your feedback.

Thank you for your attention during my presentation on premarket tobacco product applications. On this slide, you can find some links to helpful resources CTP has made available. I encourage you to ask questions

during the panel discussions later today, in addition to listen to the subsequent PMTA talks, which will go into more detail on the content and organization of a PMTA submission.

These slides and a video of my presentation, along with the presentations over the course of the two days will be posted to FDA's website in the days following the meeting. Thank you.

(Applause.)

MS. RADWAY: Thank you Ms. Busta. Next we have Ms. Sarah Amyot discussing TPMFs.

MS. AMYOT: Good morning everyone. My name is Sarah Amyot. I'm a regulatory health project manager in the Center for Tobacco Products' Office of Science. Today my presentation will focus on Tobacco Product Master Files, also known as TPMFs.

This presentation will briefly cover the following topics: an overview of the TPMF program, some key terms, how to organize, establish, amend and reference a TPMF, how a TPMF

is reviewed by CTP, and I will conclude with some key take-home points.

Let's start with an overview of the TPMF program. CTP receives submissions required by law such as health documents, ingredient listings and applications. To ensure compliance with the law, some of these documents include information that is trade secret and/or confidential commercial information from multiple sources.

For example, if a tobacco product manufacturer is providing an ingredient listing on a tobacco product but purchased a component from a component manufacturer, ingredient information on that component must still be provided. So how could the component manufacturer allow for use of this information without the right of substantial competitive harm? The recommended approach from CTP is the establishment of a TPMF.

A TPMF is a file voluntarily submitted to CTP that contains trade secrets and/or

confidential commercial information about a tobacco product or component that the owner does not want to share with other persons. TPMFs are a beneficial tool for manufacturers, component suppliers, ingredient suppliers and researchers, and can assist in the tobacco product submission process.

So how does a TPMF work? Simply, a TPMF owner allows an authorized party the right to reference its TPMF in support of a tobacco product submission to CTP. CTP can then access and review the confidential information as part of their submission, but at no point in time does the authorized party see or have access to the confidential information.

Let's look at this through an example. An ENDS manufacturer, Company A, intends to submit a premarket application for an ENDS product. Company A utilizes cherry e-liquid purchased from Company B in their ENDS device. For the premarket application, it is necessary to provide the full listing of materials,

ingredients and composition of the cherry e-liquid.

However, Company B does not want to provide that information to Company A. Instead, Company B can establish an TPMF that includes all of the cherry e-liquid information. Company B can then provide Company A authorization to reference its TPMF in a letter of authorization or LOA, and also provide a copy of the LOA to CTP.

Now, Company A can submit a premarket application and CTP can look on behalf of Company A all of the cherry e-liquid ingredient materials and manufacturing information located in the TPMF. This benefits Company A, to ensure a complete application and benefits Company B, by allowing use of their cherry e-liquid information without disclosing it to Company A.

Additionally, the TPMF program mutually benefits TPMF owners who can reference their own master file rather than submitting the information separately for multiple applications

or submissions. By allowing FDA to keep certain information on file in a TPMF, it streamlines, simplifies and potentially reduces associated costs and time related to administrative work because a company will not need to resubmit data for future applications, thus easing the application burden.

For example, if a manufacturer, Company C, utilizes the same ENDS device in 50 products, they could submit a TPMF that utilizes all of the manufacturing information for that ENDS device. In lieu of reporting this information in 50 premarket applications, Company C could reference their own TPMF.

This would save both time and reduce errors, as the manufacturer would only provide this ENDS device information once, rather than copying and pasting it 50 times into multiple submissions. In order to assist industry's TPMF submissions, FDA published a TPMF guidance in May of 2016. The guidance document includes how to establish a master file, considerations for TPMF

owners in maintaining their TPMF submissions, how other persons can use a TPMF and FDA's role in the TPMF process.

Before I move on, it is important to describe and understand some key terms. CTP considers a TPMF owner as an entity. For example, a person, company or subdivision of a company that owns the information contained within the TPMF. I will refer to the TPMF owner as "owner" for the remainder of the presentation.

Unless otherwise stated by the owner, the authorized representative is a person who is authorized to represent and communicate to CTP on behalf of the owner, and is able to make decision on the TPMF, for example to grant or rescind authorizations to the TPMF.

CTP considers an authorized party a person who has been granted authorization to reference a TPMF, which is typically obtained in writing within an LOA from the owner. This LOA, which stands for letter of authorization, is a document prepared by the owner or authorized

representative that grants a person authorization to reference a TPMF. The LOA should also identify any limitations to the authorization, for example if the owner is allowing a company authorization to reference only a certain section of the TPMF.

Now, let me walk you through how to establish a TPMF. Currently, there are no requirements for structure of a TPMF, but CTP recommends the TPMF be organized in a logical manner. The CTP electronic submission file formats and specifications document, which can be found in the CTP website, provides a recommended table of contents, format and a folder file structure for submissions to CTP, which include TPMFs.

The document contains a sample listings and hierarchies capturing the content, structure and organization of submissions to CTP. The applicable sections and content captured by the table of contents may differ by the type of application the TPMF is established for.

Additional information on the organization of submissions was provided in an earlier presentation.

Administrative items recommended for the owner to establish a TPMF include a cover letter which can be housed in Module 1 of the table of contents headings and hierarchy that contain a statement that the information being submitted is a TPMF, contact information of the owner or authorized representative, signature of the owner or authorized representative who resides in or has a place of business in the U.S.

If submitted by a non-attorney representative, include the owner's authorization. If submitted by an attorney, include attorney declaration and authorization. If the owner or authorized representative does not reside in or have a place of business in the U.S., contact information for a U.S. agent.

Additionally, a table of contents which can also be housed in Module 1, a list of authorized representatives and their contact

information, and a list of authorized parties and their contact information including any limitations to each authorization, which can be housed in Module 1.13.

The content of the TPMF may include tobacco product information such as ingredients, additives and constituents which can be housed in Module 3.2, non-clinical behavioral studies, which can be housed in Module 4.3, and abuse liability studies, which can be housed in Module 5.2.

Additional information for what to include for different types of submissions will be provided over the course of this public meeting. CTP is encouraging regulatory correspondence electronically via the CTP Portal. Electronic submission is generally available 24 hours a day, 7 days a week. Therefore, it is encouraged to send TPMF submissions electronically via the CTP Portal.

Here is an example of how to present information in a cover letter. Note that the

subject line is clear, that this submission is a request to establish a CTP/TPMF. The owner's contact information is present, the submission lists authorized parties and each company's limitations to their authorization, and the submission is signed by an authorized representative for their company.

Using the same example, here is how to present information in an LOA. CTP recommends that the applicant, Company A in this example, include its LOA when submitting an application that references a TPMF. Note that the subject line is clear that this is an attachment, that this attachment is an LOA from the owner.

The LOA includes the TPMF submission tracking number or STN. It includes limitations to their authorization and the LOA is signed by the owner. Upon receipt of a new request to establish a TPMF, CTP will review the submission to ensure it contains enough information to establish a TPMF.

As mentioned a few slides earlier, CTP

looks for several items in the request cover letter. For example, is the cover letter signed by the owner and does the file support submissions to CTP like premarket tobacco product applications or PMTAs. If the information is present to establish a TPMF, CTP issues an acknowledgment letter in a timely manner to the owner confirming receipt and establishment.

The letter identifies the owner, CTP STN, contact information for the regulatory health project manager and information on how to update the TPMF. Receiving an acknowledgment letter means the owner's file is established within CTP, and ready to be used as a reference by other tobacco product submissions. If additional information is needed for establishment, CTP will contact the owner.

We intend to work with the submitter to ensure all requested information is received. Once the TPMF is established, the TPMF can be updated by the owner and referenced by an authorized party. Let's review how to update and

amend an TPMF. A TPMF can be amended at any time. Owners may choose to add or modify scientific information or even remove authorized parties from referencing its TPMF.

CTP recommends owners include a cover letter that contains a statement that the information is being submitted as an amendment to a TPMF, original TPMF STN, signature of the owner or authorized representative. Also include an updated table of contents, a historical listing of what information has changed within the TPMF, and the information that is to be amended.

If an owner is clarifying a section with a significant amount of edits, it may be helpful to resubmit the entire TPMF or the entire section of the TPMF.

Consistent with other FDA centers, CTP does not intend to conduct scientific review of a TPMF at the time of its submission. CTP intends to conduct a scientific review of the TPMF only when the TPMF is referenced by an authorized party submission to CTP. This is because

different submissions may have different information content needs.

Let's walk through now how to reference a TPMF. CTP recommends applicants include a notation in the cover letter that the application is referencing a TPMF, and include the TPMF's STN. If referencing a TPMF amendment, include the date the amendment was submitted to CTP, if possible, where the information is being referenced is located in the TPMF, for example, the section or page number, and a valid LOA to reference the TPMF. I refer to Slide 16 on how to present information in an LOA.

If there are any questions about the content of the TPMF, the authorized party should contact the owner. Upon receipt of a submission such as a PMTA that references a TPMF, CTP will begin scientific review of the TPMF. I will now walk through how we review the TPMF.

CTP will first verify that the applicant is authorized to reference the TPMF and the extent of the applicant's authorization. For

example, is the applicant only authorized to reference the TPMF for a particular PMTA, or for all of their applications? If the applicant does not have authorization from the owner, CTP will inform the applicant of this, and CTP will not review the TPMF.

This is why it is important for the applicant to include a valid LOA to reference the TPMF. Once CTP determines that the applicant is authorized to reference the TPMF, CTP will then begin scientific review of both the application and the TPMF. When reviewing the TPMF, CTP will review the extent of information authorized in the LOA. This review, based on the reference, will result in CTP finding the information adequate or inadequate.

Let's presume that in reviewing the TPMF content concurrent with the PMTA, CTP determines that the TPMF content is adequate. This means that the TPMF information being referenced by the PMTA is sufficient, and CTP will continue scientific review of the PMTA.

Because there are no deficiencies in the TPMF information that was referenced and reviewed, CTP will not send a letter to the owner.

So what happens if CTP determines the TPMF content is inadequate? If deficiencies are found within the TPMF during scientific review, CTP will send letters to both the owner and the PMTA applicant. However, information provided to the PMT applicant is limited. The owner will receive a letter detailing each of the specific deficiencies and a request to respond within a specified time frame to amend the TPMF.

In contrast, the PMT applicant will receive a letter that will simply cite that deficiencies were found in the TPMF which have been communicated to the owner. Specific details about how the TPMF is deficient is not relayed to the applicant. Depending on the review stage, this letter to the PMTA applicant may request a time frame for response.

By following this process, CTP does not convey the specific deficiencies to the

authorized party, as to not disclose any trade secret and/or confidential commercial information. It is important to note that the authorized party is solely responsible for ensuring their premarket application and supporting documents, which would be the TPMF in this case, is adequate to support all statutory requirements.

So in the example we just discussed where a PMTA applicant is referencing a TPMF, it is the PMTA applicant's responsibility to ensure the owner responds within the requested time frame and that all documents support the statutory requirements for a premarket order. If the owner does not respond or fails to provide the documents necessary to support a premarket order, the order is likely to be denied.

We encourage the authorized party and the owner to communicate and coordinate their responses to CTP's letters, so that CTP's comments are adequately addressed in the requested time frame.

I would like to end with some key take-home points from this presentation. First, TPMFs are a beneficial tool for manufacturers, component suppliers, ingredient suppliers and researchers, and can assist in the tobacco product submission process.

Second, the applicant or authorized party at any point in time does not see or have access to the TPMF content. Third, a TPMF is reviewed when referenced by another submission. Fourth, CTP reviews the TPMF and the scope and context of the referenced submission, and lastly time lines for TPMF review depend on the referencing submission.

This concludes my presentation. I understand that was a lot of material to cover. If you have any questions after this presentation, I encourage you to ask questions during the panel discussion, which will be after lunch. You may also contact your regulatory health project manager. Their name and contact information is located on the bottom of your

letters.

If you do not know who your assigned regulatory health project manager is or if you're new and have not yet submitted a TPMF, please call -- contact our call center, the Office of Small Business, the Office of Ombudsman or send an email to askctp@fda.hhs.gov. Thank you.

(Applause.)

MS. RADWAY: Thank you to both of our presenters. Now we are going to break for lunch a little bit early, and then we will still only take one hour for lunch. So we'll be back at 12:40. Thank you.

(Whereupon, the above-entitled matter went off the record at 11:38 a.m.)

MS. RADWAY: Welcome back everyone. So I wanted to just give another reminder for those on the webcast. If you have questions, you can send them to workshop.ctpos@fda.hhs.gov. First up this afternoon will be Mr. Chad Burger discussing application-related inspections, and then we'll go into our second session of panel

discussions.

MR. BURGER: Okay. Can everybody hear me? All right, great. Thank you Anne for the introduction. So good afternoon everyone. My name is Chad Burger. I'm a branch chief in the Office of Compliance and Enforcement, and my branch is primarily concerned with coordination of inspections and support of the review of premarket tobacco applications and modified risk tobacco product applications.

Today, I'm going to discuss application-related inspections. So my presentation will discuss FDA's inspection authority, the type of application-related inspections, what you should provide in your application to prepare for an inspection, what you can expect prior to the inspection, the objectives of the inspection, how inspections are initiated and what will occur during the inspection close-out process. Also, I'll provide some resources to help with additional questions you may have following this presentation.

FDA does have authority to inspect under Section 704(a) of the Food, Drug and Cosmetic Act, and inspections may be conducted at establishments such as factories and warehouses, and may include pertinent equipment, finished and unfinished materials, containers and labeling. FDA will conduct inspections of the manufacturing sites and sites and entities involved in clinical and non-clinical research to support FDA's review of your applications.

Inspections help to ensure you can manufacture the product in accordance with the manufacturing practices described in your application, the quality and integrity of data submitted, and compliance with applicable FDA regulations. The inspections are performed by FDA staff from the Office of Regulatory Affairs, Tobacco Operations staff and Office of Bioresearch Monitoring.

The Office of Regulatory Affairs or ORA, Tobacco Operations staff consists of consumer safety officers and investigators, and

the premarket inspections are led by ORA. The Center for Tobacco Products may send representatives from the Office of Compliance and Enforcement and the Office of Science to attend the inspections as subject matter experts.

Now to discuss the type of application-related inspections. To support FDA's review of your premarket or modified risk tobacco product application, FDA may request to conduct inspections of your manufacturing sites and sites and entities involved with clinical and non-clinical research submitted in support of your application.

The two types of application-related inspections are manufacturing and bioresearch or BIMO inspections, and I will discuss both. Manufacturing or establishment inspections are performed at facilities associated with the manufacturing, testing, storage of your tobacco products in your application.

The facility should be inspection-ready at the time of inspection, or time of

application submission. So what does inspection-ready mean? You should be ready to manufacture the products subject of your application when you submit your application. FDA investigators will request to observe the manufacturing process for those products during the inspection.

The purpose of these inspections are to verify the accuracy of the manufacturing information submitted in your application. The number of investigators and the number of days to perform the inspection may vary depending on each inspection. Manufacturing inspections may be performed at domestic or foreign establishments.

For foreign inspections, documents that have been pre-requested by the agency and written in a language other than English should be translated into English prior to the inspection, and should be accompanied by a science statement by an authorized representative of the manufacturer.

Additionally, the firm should arrange to have an on-site translator for application-

related inspections that occur in countries where the primary language is not English.

BIMO inspections may be conducted at sites with clinical and non-clinical studies submitted in support of your application. The purpose of the BIMO inspections are to verify the accuracy and reliability of data submitted to FDA in support of your application, and to verify the rights, safety and welfare of human subjects who are protected during a study. An FDA Form 482 Notice of Inspection is issued at domestic establishments only.

Now that you know the type of application-related inspections, I will discuss ways to prepare for an inspection. For manufacturing inspections, the FDA requests a full description of each manufacturing and testing facility involved in the manufacturing, packaging, storage and testing of your new tobacco products. This also includes manufacturing facilities that manufacture products for further manufacturing.

The description should include each manufacturing and testing facility's address, point of contact, assigned firm establishment identifier or FEI number, with a description of the manufacturing steps performed at that facility. If there are multiple facilities manufacturing, involved in the manufacture of your product, you need to provide a comprehensive description of all manufacturing and testing activities, processes and controls performed at each of these facilities.

It should be clear what manufacturing steps are occurring at each facility for each product in your application.

Biotesting accreditation information should be submitted for the testing sites that perform testing activities on your products subject to your application. A list and summary of all standard operating procedures and examples of forms and records for all manufacturing and testing activities should also be submitted. If available, the production schedules at the

facilities for the final products are manufactured for the first four months after the date of submission of your application should be submitted.

If FDA determines that a manufacturing inspection is necessary, the production schedules will be requested for each facility chosen for inspection. The investigators will request to observe the manufacturing process during the premarket inspection.

Now I will discuss what to provide in your application to prepare for bioresearch monitoring or BIMO inspections. For studies that you conducted or that were conducted on your behalf, you should submit a list of all studies submitted in support of the application. It's very important to submit, to identify the key pivotal studies which you're relying upon to support the issuance of an order.

A list of all sites and investigators that conducted the study, including contact information and addresses, all versions of

protocols and amendments that were used in the study including investigator instructions, if any were produced in addition to the protocol. Line data also known as data line listings, including data definition files that include the names of the variables, codes and formats in each data set.

You should include a location of all source data, a list of all contractors who participated in the study including the role of each contractor, initiation and termination dates of the participation of each contractor, and a full report of all findings.

Continuing with BIMO, you should also provide documentation of all actions to ensure the reliability of the study and protection of human subjects. This includes documentation of study oversight by an Investigational Review Board or IRB, documentation of informed consent procedures, also documentation of good laboratory practices.

All versions of study materials, for

example consent forms or questionnaires that may have been used during the study, all versions of individual case report forms related to participant death, other serious and unexpected adverse experiences, withdrawals, and participant discontinuation where the participant was exposed to your tobacco product and are subject to your application.

So what should you expect before an inspection? To ensure that the appropriate records or personnel will be available before the inspections, the firm's clinical and non-clinical investigators will be notified by FDA prior to the inspection start date. FDA intends to utilize the results of inspections to verify the information contained in your application, and to verify information contained in any additional applications you may have filed that reference the same manufacturing sites, and clinical or non-clinical research investigators.

Failure to grant FDA access at a reasonable time and a reasonable manner, an

opportunity to inspect these sites and have access to copy and verify records pertinent to the application, including the opportunity to observe the manufacturing process of the tobacco products subject to your application may result in delay of FDA's review and decision on your application.

Manufacturing inspections are pre-announced. It may be months ahead of time and inspection may include multiple facilities. The notice will include the facilities FDA plans to inspect, a request confirming or confirming the production schedules for the manufacture of the tobacco product subject to your application, instructions for providing information the agency, what to expect during the inspection and a response date to provide a response to the notification letter.

BIMO inspections are pre-announced within a week of the inspection. The notice will be provided to ensure the clinical investigator for the study will have the appropriate study

documents available for the inspection. The objectives of the inspection are to review processes and procedures, observe and evaluate operations for manufacturing inspections, document and collect information, identify violations for manufacturing inspections.

For BIMO inspections, the FDA may identify inspectional findings. We'll communicate potential violations and inspectional findings to firm management, and we'll document any proposed corrective action plans.

So what should you expect when FDA arrives at your facility for inspection? When FDA arrives at your facility, the investigators will meet with the most responsible person on the site. They'll present their credentials and they'll issue an FDA, a Form FDA 482 Notice of Inspection, and again this is only issued at domestic establishments only.

So what's covered during your application-related inspection? For manufacturing inspections, the investigators may

request administrative information such as firm history, legal status, organization charts, number of people employed, hours of operation and names of top officials. A walk-through of the facility may occur, but may include a visit to the manufacturing, testing or storage areas.

Investigators will want to observe the critical steps of the manufacturing process and procedures for manufacturing and controls of the product. Labels labeling advertising and packaging for the product subject to the application will also be reviewed by the investigators.

For BIMO inspections, the purpose is to verify data submitted in the application and human subject production. During BIMO inspections, FDA will review administrative information, conduct a data audit including protocol, amendments and deviations, informed consent processes, source documents, case report forms, adverse events and test article accountability, and also they will conduct

facility and equipment assessments.

Note that this list is not all-inclusive. The investigators may request additional information during the premarket inspection.

At the conclusion of the application-related inspection, the investigators will perform a closeout. This will include a summary of the inspection and discussion of issues identified or observations with management. If a Form FDA 483 is issued at the closeout of your inspection, you should provide an initial response in a reasonable time frame on a plan to correct the observations or inspectional findings.

Resolution of 483 items do not need to be resolved at this time but should be resolved before the end of the review cycle. Note that a FDA 483 are not issued at BIMO inspections. Instead, BIMO makes reference to inspectional findings. Wait a minute, sorry. I was on the wrong slide.

So final report. An establishment inspection report or EIR will be written for following the inspection. This report will describe the information discussed and collected during the inspection. A copy of the EIR will be sent to the most responsible person identified during the inspection. This will occur after a decision has been made on your application.

And here are a few resources to help you with any questions that you may have. Thank you.

(Applause.)

MS. RADWAY: Thank you, Mr. Burger. So now we will start our second session panel discussion. Can I ask the panelists to come up and take a seat? I wanted to note that we did change one panel member for this session. Ms. Charlotte Owen is not able to be here, so Dr. Mike Ogden took her spot.

So as a reminder, each panelist should introduce themselves and limit their remarks to five minutes.

Mr. Burd, you can start.

MR. BURD: Hi. Good afternoon, everyone. My name's Kevin Burd. I'm the Business Development Director for a company called CNT. CNT is the largest global supplier of nicotine in the world. We supply through brands CNT as well as Siegfried and Nicobrand. In fact, I think 100 percent of the approved products in the pharmaceutical sector comes through our supply chain. In addition to that, we have significant tobacco product master file in the ENDS space.

Besides CNT, I also work for another company called Chemular. Chemular is a group of regulatory consultants comprised of some ex-FDA officers as well as colleagues from pharmaceuticals and the tobacco medical device sector, where we're guiding companies through the PMTA process.

So with that, we have a number of mainly small to medium customers that work for -- that come to us for PMTA guidance. And so quite

often some of the questions I just want to put out there for the presenters were -- that we get asked most often, and I selected a few of those.

Often we get asked about making small changes to their product, and including changes like the manufacturing location, or if they're making a supplier change.

And so it seems that there's not a lot of guidance on the ability to make those changes prior to the PMT application process, so we would like some advice or guidance from the FDA on that. In addition to that, if they could supply us with what comparable data the FDA would expect if you're not just making a change but selecting an alternative supplier, in case you want to have two suppliers for the same product.

In addition to that, we wanted to ask on the guidance which may come up in a future presentation, I'm not sure yet, but on the expectations of validation in the manufacturing process in particular. We see a lot of validation discussions throughout the PMTA

guidance documents for method validation. However, when it comes to manufacturing process, process validation, things like we might see in other industries like medical device where you have an IQ, OQ, PQ or PPQ, it seems to be missing for the PMTA guidance.

So we'd like to have some understanding of what the expectation is for those companies going through this process for their manufacturing. Thank you.

MR. OGDEN: Well, good afternoon, everyone. I'm Mike Ogden, Senior Vice President of Scientific and Regulatory Affairs for RAI Services Company in Winston-Salem, North Carolina. RAI Services provides scientific and regulatory engagement, particularly in this context, FDA submissions for all of the Reynolds American Tobacco operating companies, which includes R.J. Reynolds Tobacco Company, American Snuff Company, Santa Fe Natural Tobacco Company and R.J. Reynolds Vapor Company.

As a last moment fill-in, I don't have

any prepared remarks before the day. But I jotted a few notes over lunch and did share a couple of perspectives that I have shared in these types of forums before. One of the things certainly that I would expect and hope for throughout the scientific review process of PMTAs is transparency from the agency, and equitable treatment for all applicants, be they large or small, domestic or international. I think that certainly is very important.

Another point to make, which everyone in this room is aware of, is the very constantly moving bar in this space. And that bar is moving in two dimensions. One is time, which we've seen the filing deadline for deemed products that are currently in the market, has moved by my count five times over the last three years, now set for May 12 of next year. But also we see a moving bar on content, and that is based on previous guidance, draft guidance from the agency, the final guidance in June and even the proposed draft rule on PMTA.

We saw some of that this morning with some of the content. Some of the format is continuing to move, and hopefully I think the expectation is that applicants will take the -- take the available information and make their best effort possible. I certainly would hope that the agency would be mindful of that moving bar, and the time it takes to get ready to meet a bar that you were planning to meet a year ago, and that some of these new content and format structures I would hope and expect would not be applied retroactively, because that would be fatal, because you can't comply with a format or a content requirement today that you don't know about until tomorrow.

So that one is something I would hope would be the case. The other thing I would advocate for, particularly as the SE process has evolved over the last ten years or so, is that in that space we as applicants have seen the agency's thinking evolve over time from one application, same type of application for one

product to another that spans a year or two, that there is evolving thinking about the type of science that may be required.

And in many cases, I think it's fair to say that applicants have been faced with requests from the agency that the applicant either did not or arguably even could not have anticipated. I would hope not to see that play out in the PMTA process, particularly for ENDS, where we don't have any perspective I think to really share. We're kind of learning this together.

So with that as a backdrop, I'm happy to participate in the panel and either ask or answer any questions that I can. Thank you.

MS. STARK: Hello again. My name is Cristi Stark for those of you that weren't here for the morning session, and I am the director for the Division of Regulatory Project Management. I'm going to save the questions for panel discussion and just turn it over to Lillian.

MS. ORTEGA: Good afternoon. My name is Lillian Ortega and I'm the Director of the Division of Enforcement and Manufacturing. And as Mr. Burger presented right before the panel discussion, we work closely with Office of Science to coordinate manufacturing inspections as well as bioresearch monitoring inspections. We work closely with the Office of Science to identify the facilities in which we inspect, as well as the data that is -- that needs to be verified. And I look forward to the panel discussion.

MS. RADWAY: Okay, thank you. So we did get a lot of questions so far but continue to write down your questions and send them forward. So the first question is referring to deemed products, how should minor safety and consumer improvement changes between 8/8/16 be handled, and connecting supporting data for a product that will subject of a PMTA for deemed products.

MS. STARK: I'll start, and I hope I get the question correct. I'm going to reframe

it a little bit.

So for people that may not be aware, August 8th, 2016 is an important date. If your deemed product was in interstate commerce within the U.S., that product can be marketed right now in the absence of an order if it's new.

If you modify that product after August 8th, 2016, that requires authorization prior to delivering that product into interstate commerce for commercial marketing. So if I heard the question correctly, we're looking at two things. One is a safety concern and one is improved consumer use. And I'm going to parse out the two.

Our goal here at FDA is to protect the public health. Anything dealing with a safety issue, we want to accommodate and work with you now. So if there is an issue around safety, please get in touch with us and we can work out with our offices here a case by case approach moving forward. We don't want to have some sort of product after that can cause any type of

health concern. Both the Office of Science and the Office of Compliance and Enforcement work together with those cases.

With respect to improving consumer use, that might be a little bit different. So again, for those cases, we may look at an interaction with quick touch base with your project manager. We may potentially look at a meeting or there may be another option forward such as submission of an application.

If you currently have a PMTA in-house with us, we can talk about options for some of those changes, because that change would be a new product. We'd have to look at those options moving forward. If you don't yet have one, then maybe you want to look at putting in the product that you want marketing authorization on. I think I hit that. Do you want to add anything?

MS. ORTEGA: Yes. I would echo what Cristi just mentioned, is that if it's a safety issue, as Cristi mentioned we would definitely work closely with the Office of Science in

reviewing the information, as well as you identified that what the safety concern is, work with the RHPM so that we can -- we can identify the risk that it may have to the public health again.

Our goal is again to protect the public health. If your product has, needs to be changed in any way, the best approach is to contact CTP through Office of Science so that we, the Office of Compliance, can work with Office of Science to identify your product prior to making changes to the product.

MS. RADWAY: Okay, thank you. So we've got a number of questions related to ongoing studies and submitting amendments, and so I'll just read one.

Based on limited time frames companies are working with, the length of studies and the capacity constraints of CROs, can a pre-May 2020 submission be made and then supplemented with data when available?

MS. STARK: Okay. So I'm going to

just call it out right now. When we review an application, we want it to be complete for us to do our review and issue a decision within the time frame that we've been noting on the screens. We have 180 days for us to actually issue these decisions on a PMTA upon receipt of that complete application.

If a manufacturer is still running a study for a pivotal end point, and they have interim data that they choose to submit and then later decide to amend their application with the final study results and additional significant data the agency has not yet reviewed, that could be construed as a major amendment, which would reset that 180-day clock.

I say this now. I want to be very clear, because we're looking at a May 2020 deadline, and I want people to understand what they need to get in now for the agency to review. I'm also going to encourage individuals to review the presentations later today and tomorrow regarding content, scientific content for these

applications, and then potentially asking questions in later sessions to other members of senior staff within the Office of Science regarding that specific material.

But I do want to note that if there's significant information that is received that the agency previously has not been reviewing, that could trigger a major amendment with a reset to the clock. If the clock is reset, that may go past that May 2020 date, which could have serious implications for a product that may currently be on the market as of August 8th, 2016.

I also want to echo one of the questions that Mr. Burd asked earlier to get going. There are some questions regarding change in suppliers, change in manufacturers and locations. I actually, and I'm hoping for Dr. Ogden's experience as well, with some of the applications that have come in for other types of products.

The way that the statute is constructed, any modification creates a new

tobacco product. A new tobacco product requires authorization prior to getting out there. But I want to note that sometimes when you change a supplier, you may have different sources. So maybe it is not traditionally a supplier change, which is why I'm looking for some advice.

Sometimes there's middlemen that we go between, and you may think that there's a change in that source but you're actually not making modification of the product. In those cases, it's good to look to see is it truly the same or is it a different, a different material that goes in or ingredient, because that would change if you have a new tobacco product or not.

With respect to a change in manufacturing location, we're going to have to look at that specific case because you may decide to manufacture on the west coast, and then decide you want to move it to the east coast. If your manufacturing is the same, you've performed your validation for your different facilities and the ingredients going in and what is coming off the

line are the same, including taking a look at your constituents, then you should have the same product.

Therefore, that change in location should not alter and should not create anything that we need for a new tobacco product. I'm going to look for others in the panel to comment.

MS. ORTEGA: I would also add for changes in manufacturing location, if that occurred either prior to or depending on the time line in which you submitted your application, we would be looking for in the Division of Enforcement Manufacturing when we go out to inspect, we would be looking for the timeline in which you changed that manufacturing location, and identify what were the changes that occurred, what were their -- the reasoning for the manufacturing location so we'd have a better understanding when we go out and inspect what changes in your processes occurred during that time frame.

MR. OGDEN: Since Cristi called on me,

I'll jump into this. Actually, I do have a view. It's a view from the Reynolds side on both questions that Kevin asked. In my view, as long as the manufacturer's specifications are met, geography and supplier should not matter.

So for an example, if we've got a neat ingredient, a single CAS number and if we have as our specifications is minimum 99 percent purity. I'm just making this up as a hypothetical, then our view, my view would be that sourcing that component or that material from any source is acceptable. It meets our specifications.

To the geography question, I would treat it the same way. If you've got reasonably precise manufacturing specifications, if they are met it matters not where. You have made the same product and that is the approach we have taken for a decade now and it seems to be a reasonable approach, at least in our experience with the agency.

MS. RADWAY: Thank you. Do you want to add something?

MR. BURD: Sure, yeah. That's quite -- I think just as companies are going through the process of the PMTA, they're having to ask more long-term questions that they probably haven't thought of. I know some of those questions are well, I'm going to have to purchase from the supplier for the next decade or longer. And so they're trying to ensure that those are de-risking that by maybe having an alternative.

And so with the alternative, there's always the question of now do I need to conduct separate trials with both products from different locations? And so that makes -- this becomes a nightmare. But I like, I do like the answer. Look, if you have the specification, you set it for a reason.

MR. OGDEN: That was my answer.

MR. BURD: That was your answer. I'd like to make sure that the FDA's okay with that answer, but that's a great answer.

(Laughter.)

MS. STARK: So let's talk about if

it's different, okay, and just slightly different but it's different. So you're off, you have a different target value. You're slightly outside of your specification range. What do you do in that case? Let's say that you have a PMTA that's been authorized. Depending on what the differences are we have options where you can do a streamlined, a supplemental PMTA depending on what that is.

So what you could end up doing in that option is you would end up submitting a PMTA. You would reference the original one that was authorized, and you could work with the agency to determine that you've hit the filing criteria. By your cross-reference you're going to hit the majority of what's in 910(b). We'll have a sample letter go out if samples are requested or not. But what is going to be incredibly helpful is having your side by side comparison for here's my old product, here's my new one with the changes and the differences, and then any other supporting scientific rationale that you would

need for that alternative type of ingredient or material, whatever you're looking at for these.

That way, you're not re-doing all of your studies. You're really going to be looking at a smaller, leaner amount of data. So that's an option with the PMTA. We also have that with the SE program. There's other programs where we can look at a little bit less data.

I want to note though if you're authorized through a PMTA, the SE program will be off the table because you don't have an eligible product hit. But you could take that authorized PMTA, and let's just say it's an additive change. Submit it through your exemption request program. If you are removing or adding or increasing or decreasing the existing quantity of that additive with that little minor modification, an exemption request may be appropriate.

So I'm just giving you ideas for how to handle this, where you're looking at additional types of minor modifications.

MS. RADWAY: Thank you. Okay, next

question. If denied, what is the timeline to take products off of the market, and if denied but plan to resubmit, is there still a recall protocol?

MS. STARK: So I'm going to start, and then I'm going to hand off to Lillian, because we tag team on these. So the one thing is I'm going to encourage you, any time you receive correspondence from FDA, please read your letter. For all of our order letters, we've been very clear with what will happen. We've already had experience with provisional reports in the substantial equivalence program, where they were legally marketed.

When they were found not substantially equivalent, they had to then be removed from the market. What we had was steps within the order letter for who they need to contact and time frames regarding what we do with the product, because there are several options available and many of those steps start with the Office of Compliance and Enforcement.

So my biggest key message to you is when you get that letter, please read it and I'm going to turn it over to Lillian.

MS. ORTEGA: So as Cristi pointed out, we work closely with the Office of Science in drafting the letter. Office of Compliance and Enforcement, once a letter is issued, the enforcement of that letter is our responsibility. We work closely in identifying what the next steps are. If you receive an order of a non-marketing -- sorry, marketing denial order, there will be specific instructions on your next steps.

Expectation for your product. As you read the order, if you did not receive authorization, then your product is unauthorized. So there are next steps, and we want to communicate directly with you on your next steps, what your plans are, if you do plan to address the order or discrepancies in the order, we will be in direct communication with you as well as Office of Science. We'll work with you all. But the expectation is that your product is

unauthorized at the time.

MS. RADWAY: Do you want to go?

MR. BURD: Just wanted to comment as well. So with that, and we do get asked this, how do shop owners know that a company is going through the PMTA process? Is that -- is that to be published or just because there's a thousand products on the market. How do they know which ones they're allowed to stock and which ones they're not during this review period?

MS. STARK: So the submission of a PMTA is not information that the generally hands out, and this is similar to other centers. When a BLA or an NDA or a PMA is submitted in, depending on if you're looking at devices or biologics or drugs, typically the shop owners may know through a myriad of resources.

One, the applicant submitting it may actually make a public statement. You heard in the first panel session today one of the presenters up here talking about a public statement for applications that were submitted to

the agency. There may be press releases.

Second, when the agency makes the decision, if we're going to authorize, what we have been doing when we have gone through the 508 compliance and other things for posting as you saw in an earlier presentation today, we try to post the decision summaries as well as the order letters so shop owners are aware.

For the cases in the deemed products that were on the market as of August 8th, 2016 and they would have to be removed from the market if not authorized, because we haven't yet hit there we can't talk about what will happen in the future. But I can give you an example of what we've done in the past.

For provisional reports where those products were legally marketed and then when they received a negative order, they had to be removed, we would actually post on our website that decision for that negative order. We would post the redacted copy of the summary review summarizing that, and store owners were then

aware through that process.

The other thing is the Office of Compliance and Enforcement has also been helpful with outreach or if there are questions coming through and I'm going to turn it to Lillian to add some of those.

MS. ORTEGA: So what we usually do, what we do for NSE or non-substantially equivalent orders or negative orders that are issued by the agency is that we do list those products that have been identified. That is something that our retailers have found to be extremely useful as far as identifying what can be on the market and what can't be on the market.

So that is one of the ways, and we'll be working with OS in identifying the best way to move forward and put those products that are unauthorized on the web page, so that the retailers as well as shops can -- big shops I'm assuming, can have that information forthcoming.

MR. OGDEN: Well I thought Lillian, I just heard you say something different than what

I heard Cristi say, so let me ask for a clarification. So for a net new product to market, I fully understand FDA's -- your statement Cristi and the obligation there. That's private between the FDA and the applicant, unless or until it's ever cleared, then it becomes public.

But in the case where we have the deemed products that are already on the market, with a deadline of May 12 for submission, it's very analogous to the provisional SEs of March 21 of 2011. So in the current case, if an application the way I look at it, if it's not been submitted to the agency by May 12, on May 13 it is illegal. That is something that I think FDA should take the leadership position in in how to get that information to retailers, to wholesalers, to the general public, to know -- and I know you can't do it in a day. But within 30 or 60 days, it seems like that would be something that the agency should take the lead on, is to make sure that those products are --

it's known what their legal marketing status is. Is that what -- did I hear you say that Lillian, or did I misinterpret?

MS. ORTEGA: No. That's exactly. We're interpreting that, so we're not going to speak to the current compliance data, and technically I will say that the 8/8/16, the August 8th '16 products are technically under enforcement discretion as we speak right now. So they are violative as by statute.

But they are under a compliance, compliance policy right now until that May 12th, 2020. But the goal is that we would be providing information as we are allowed, to the list of products that are, haven't -- we have not received applications for.

On how best to do that, we would work closely with Office of Science in identifying that, because we can't -- as you stated, we can't turn that around in a day, and the universe of product that we currently have on the market, as well know, are in the hundreds of millions.

MS. STARK: I want to also put a flag in for others to be aware that there are other regulatory requirements for which you must comply. So we are looking at that across the board and not just submission of the application. So one such example is we should have received an ingredient listing, whether you are foreign or domestic, for all of these products that are under a compliance policy.

MS. RADWAY: Okay, thank you. Next question. Will CTP rule that all flavored ENDS except tobacco menthol are not protecting the public and therefore reject?

MS. STARK: Okay. So this is a fun question. So you know what we know, what you see out there in the news. What I can tell you is we are receiving applications now for all ENDS, regardless if they have no flavor, mint, menthol, cherry, whatever you call it. Submit it to us; we are happy to review it and provide decision.

That is not a basis for any type of rejection. Our acceptance criteria was presented

in slides this morning, and you could see through that flavors had no part of acceptance within that. I can tell you when you look at filing criteria, you will need to provide your ingredient list, your characterization of your product in order to make it through filing. But again, that's the content for us to get into the substantive review. So we want to review your applications for flavors and non-flavors for these products.

MS. RADWAY: Okay, thank you. Next question, how many ENDS RTAs included lack of EA?

MS. STARK: So the slides presented earlier from Ms. Busta had a very large number of RTAs for ENDS products. I'm going to note that the ones that were provided in the cumulative metrics, a significant percentage, so at least 80 to 90 percent were RTA'd due to lack of an environmental assessment, and let me define that.

There was nothing in the application. So it was just silent. If you do not have an environmental assessment in there, that is a

basis for a refusal to accept. Not just for PMTAs; also for exemption requests and for substantial equivalence reports. So please, please, please make sure that's in there.

MS. RADWAY: Okay. We've got a few questions related to TPSAC and PMTAs, so I'll just read one. Does the FDA foresee the need to refer any of the ENDS PMTAs to TPSAC, and what criteria would FDA weigh when deciding on this referral?

MS. STARK: So unlike the modified risk tobacco process where each application is to be referred to TPSAC, this is not a requirement for a premarket tobacco product application. Everything will be case-specific and really what the agency's going to be looking for is do we need to solicit particular advice from that committee?

If a manufacturer would like for the application to be referred, we're going to be asking for the rationale to support it and we may or we may not agree with that. I want to note

that this is not the only panel that FDA has. We have experience in other Centers where manufacturers have requested panel advice and FDA has declined, or FDA has decided to go and receive panel advice even if a manufacturer does not want to go to the committee.

It's going to come down to the case. If there is something novel, where we may want to seek advice, that would be an excellent opportunity to go and ask questions of the panel. It will really depend at that point in time with what we are looking at. I hope that hits it.

MS. RADWAY: Okay. A TPMF will not be reviewed until referenced by a PMTA. Can we submit our TPMF for a pre-review by CTP before it's officially referenced?

MS. STARK: Okay. So a master file, the entire point for Tobacco Product Master File is to protect trade secret or commercial confidential information from an applicant that may want to use that in support of their application. That's it. So it's basically

putting a firewall between that information and the applicant, where FDA gets to review it on behalf.

So let's think about it in a completely different manner. We saw from the presentation earlier on process that if we were going to have a significant amount of information placed into the PMTA at a later date, that could trigger a major amendment. The same thing holds true with a master file.

So if somebody has decided I want to do my clinical study for a major pivotal end point under my master file and submit interim data and then later on when I've been reviewing the application amend it, that's going to trigger a major amendment, likely the same circumstance as it would if you didn't have a master file and you were looking at it under a PMTA. A master file is not to circumvent the major amendment. The master file intent is to ensure that information can be used without giving up that trade secret or confidential commercial

information.

So if we think about it like that, you can see that the same rules should apply for the master file as they apply for the PMTA. You should have everything in place when FDA is doing that substantive review.

MS. RADWAY: Thank you. All right. I want to direct this question to our industry representatives, and Cristi kind of hit to this point, but I want to see if you guys can give a little bit of your experience. This question says, please explain the purpose of a TPMF when an applicant can't access the information? Wouldn't the applicant just find another avenue? Do either of you have experience with TPMFs or insight to add?

MR. BURD: Yeah, okay. So I'll give two different examples. So in one example would be, you know, for our nicotine, which is probably the most referenced TPMF and will be for this category. If -- so in that situation, you might be able to select an alternative as well, and

like we discussed before, ensuring that the specification is met.

So in a case where something like nicotine, where you're -- it's a single CAS number. It's probably a little bit more of the easiest one because you're -- most of them are going to like a USP standard and you can have a set specification and do several measurements and be sure that the alternative supplier is able to meet that.

We have had some challenges with customers recently, especially in the ENDS category who are producing liquids. And so sometimes they're having four or five or six different flavor suppliers supply them flavors which they then mix to make one finished product. In some particular cases, those flavor suppliers have not been very keen to release their CAS numbers for how they make their formula.

In a few cases, one of the flavor suppliers went to great depths to do in vitro studies to ensure that they had TPMFs for their

product. However, they were not keen to release that. The challenge for the customer was that they had -- that was only one of maybe five flavors that went into their product.

And so in that case, it took a lot of contracts put in place between ourselves and the customer and the flavor suppliers, to ensure that that confidential information was able to remain confidential, yet we could get the information we needed to put together the tox analysis and all the requirements of the PMTA.

In some situations, some of the customers decided that it just wasn't worth it, and that they were going to go ahead and either just discontinue that product when the deadline comes. So those are some challenges. I think part of this is -- and I guess with my nicotine hat on and I'll do a little bit of sales pitch, but we've been doing this for 30 years.

I think when you come into an industry like ENDS, you really need to be making these long term decisions about and take very carefully

who you're doing business with. And then once you go through this process and start the PMTA, we would highly suggest that you put in place long-term supply contracts, especially ensuring change to that future, you know, product that you're buying, that you have substantial notice so that it doesn't impact you later on even if you did get approved, to make sure a year from now they have some regulatory issue that caused you to come off the market. So I would look at that as well, yeah.

MR. OGDEN: I'd like to weigh in on that as well, and FDA has been making a pitch for TPMFs for at least a year and a half in a very proactive way. I have been expressing my concerns for at least the same amount of time, and I'll do that again here, because the analogy for the TPMF is that it's a black bag, and I don't know what's in it.

As a major manufacturer, that causes me great concern, because Reynolds is a large manufacturer. We work with hundreds of suppliers

of complex materials. We have for decades, large, small, and we see mistakes made all the time, simple mistakes, calculations, use the wrong density to correct a volume to a weight. My grave concern is that if a TPMF that goes in for a material or a complex ingredient formulation that we don't know what's in there, what's the outcome if there's a mistake?

And that's -- I'd actually like to ask that as a question, because there are examples of this certainly in the SE space. So my question would be if there's a TPMF that we as an applicant rely on and it contains a calculation error, and then our PMTA is subsequently authorized, and then the calculation error is found, what's the impact on my cleared application?

Is it immediately rescinded, or what works? So that's a concern that I've got, and I'm not -- I'm not casting aspersions on anyone's ability to make simple mathematical formulations correctly, because I said we've seen small

manufacturers make mistakes. We've seen large suppliers make mistakes. We have made plenty of our own mistakes that we've had to go back and correct.

So that's my concern. So what happens if a TPMF has wrong information in it, and then how does that impact a decision being made on a product that the applicant has standing in front of the agency?

MS. STARK: So our goal is to ensure that we have accurate information to make decisions and we're human, so everyone makes mistakes. We make them when we submit applications. FDA has made mistakes when we review applications, and this is why it's a two-way process.

If we find later that there's an error within a calculation for a TPMF, we're going to start to dig to ask what is it around. If that error results in changes to the actual product that is authorized, so I'll give an example. Let's just say that there was an error with

calculation with your tobacco blend and your target value has changed, you're outside of your specifications due to this error that's in the file but it's been authorized.

There are a couple of options that the agency's going to look at. Number one, we're going to look at where are we in the process of reviewing it? If it is still under review with the process, we can actually work with the manufacturer to try to fix that before an order is rendered. If it's after the order's been rendered, we have to look at what the options are.

In cases with errors in the past, we've worked with applicants to ensure that we can review another application. We've looked for case-specific places where we could have a compliance policy for products that are out there, and we have issued orders and rescinded incorrect orders at that point in time.

We cannot make an open promise for what we're going to do because everything is

case-specific. But we do understand that there are errors that occur, and our goal is to ensure that we correct them and make sure that it's appropriate moving forward.

With respect to the examples given and the experience with master files, I hear the concern about the black hole. I heard the concern this morning with electronic submissions and how we're tying across different items. I still would like to do a plug, and I'm just looking at a company in general. We have two people up here with a lot of experience, with a lot of things that can go into a master file to support multiple applications.

So one of the ways to reduce that black box is to submit the master file and use that as a reference for your PMTAs. You have your one manufacturing process that you have that encompasses 50 products. You would actually cross-reference in your submission for your 50 PMTAs to that one TPMF.

Through that process, we are going to

go through. We will check if we need to do inspections. We're going to verify when we're out there. We will look at the -- we will look at if there's calculation errors, ask clarifications and do our review.

It is a nice way for us to work through the master file process, work with you back and forth to ensure that we make it easier over time, because I do hear you with the idea of a constantly moving bar both with time and with content, and for us to try to make this an easier process as we go forward with more experience. Your thoughts on that?

MR. OGDEN: Well I certainly appreciate the attraction of the TPMF, but I hope you and others appreciate my apprehension over it. So I'm just not there yet. I would love for it to work. I could see it working well in our case; for example, I think the case was made this morning by Leanne Campbell, if we've got a single study that we want to rely on in multiple applications, it makes sense.

But then we're in the driver's seat. If we make a mistake, it's on us. But at least we know what -- we know that it was made. We know what's in the TPMF. We know how it impacts all of our products. If it's completely outside of my or our control, that's what causes me pause. And I'm just being candid. I'm not comfortable with that yet. Maybe I'll get there with time. Who knows

MS. RADWAY: So with that, we go to our next question. What are the implications of amending an TPMF that a PMTA is referencing? Is it a major amendment?

MS. STARK: So I'm going to go back to the earlier comments, where just remember the purpose of that TPMF is really a firewall to protect that information. So when you're asking these questions about the master file, think about it in terms of if you just had a PMTA. What are the ramifications if you were to amend that PMTA? Is it major or not?

As we heard earlier, FDA may issue

deficiency letters, and some of the deficiency letters may ask for a lot, which would trigger likely a major amendment because it's substantial information that's not previously been reviewed by the agency. If there are unsolicited amendments that come in, the agency is not obligated to review them and may choose not to when going forward to make a decision.

So to answer the question, it's going to depend on was the amendment solicited? What is the content of the amendment? Has it previously been reviewed or not?

MS. RADWAY: Okay. Will CTP provide a list of all TPMFs on the website as CDER does for DMFs?

MS. STARK: At this time, CTP is not proactively publishing any of the TPMFs that have been submitted in. We are looking at all options available, but we are trying to respect the business practice for many of these companies and protect any information that might still be commercial confidential or trade secret.

If there are ideas, we are happy to take them and see what we can work through. Any ideas from the two of you up here?

MR. BURD: I mean, I do like the -- I like the DMF. There tends to be a lot of confusion when people say well, go look at the DMF and you go and search it on and then it tells you that there's listed, but it doesn't actually -- it's not very clear that the product has actually been approved.

So you know, for example, with nicotine, there might be five or six manufacturers out there but only one is actually getting used in products that have been approved. And so I think there's a challenge when companies are trying to look that up. But if that could be clarified, that would be great and I do think that list is helpful, you know.

Maybe it's something that companies that are submitting it, a TPMF. It could be a tick box on the application that allows them to make that public.

MS. STARK: So one of the things that we're looking at with Tobacco Product Master Files is the type of content that's coming in. So you're giving an example of product-specific information under a drug master file, and you're tying it to a drug approval. One of the things that we're looking at here is you may have a non-clinical study come in for your TPMF; that non-clinical study may be applied differently depending on the type of product, the route of administration, exposure, length, all of that.

So it's going to be very hard to tie that study to a particular authorization for products. But we're open to ideas and these are some of what we're looking at before we make a decision to place information out into the public forum.

MR. BURD: Yeah. I'm trying not to have a separation between industry and FDA. But even with our regulatory group that we're doing a lot with, it's still difficult to understand the best strategy to make use of that TPMF. I'm sure

over the next couple of years, it will become more clear, more useful.

I think some of the biggest challenges our customers face right now is the, you know, once they go through this process, will their product be relevant, you know, for what's currently on the market? I think those are the -- so trying to figure out not only that but also the studies that are going into this is -- but I'm sure it will come with time. So it is a good idea.

MS. RADWAY: Okay, thank you. The next question. Is the FTC going to be involved in inspections related to marketing and packaging?

MS. ORTEGA: I'll take that one. So as Mr. Burger presented in his presentation, the inspections that are conducted are conducted by the agency, the Food, Drug and -- I'm sorry, FDA. The labeling, advertising, marketing information that is reviewed during inspection is reviewed in accordance with the regulations that FDA

enforces.

So we don't have outside agencies conduct inspections with FDA. So these are again FDA inspections, and they're coordinated with the Office of Regulatory Affairs, as well as Office of Compliance and Enforcement and Office of Science.

MS. RADWAY: I have one more for you, Ms. Ortega. How will the FDA address, handle inspections of imported product manufacturers overseas?

MS. ORTEGA: So as Mr. Burger presented earlier, the applications as we receive them, we inspect domestic and foreign manufacturers. So if they are an importer of record, the expectation is with the application submission that we would get information about all foreign manufacturers manufacturing entities, as well as testing entities outside of the U.S. Those would be subject to inspection as well.

MS. RADWAY: Will the May 2020 timeline for submission of PMTAs apply to all

other tobacco products, or only ENDS?

MS. STARK: So I want to make sure I heard that right. The timeline for submission of deemed tobacco products is May 2020, and I want to note that deemed tobacco products include cigars, water pipes, pipes and others that may not fit into those categories. So I want to make sure that all manufacturers for deemed products are well aware of those timelines if they have a new product out there.

MR. BURD: And just to clarify too, you know, so that once the May deadline hits, they have 12 months to complete that application process. If there's maybe one or two or several 180-day extensions, you can only get two is my guess, and then you're likely going to come up against the May 2021. And if you come against that date and are still not completed, then you would need to come off the market; correct?

MS. ORTEGA: So, yes. Technically, that would be the case as of the May 2021 deadline. If the application has not been

reviewed and you've not received an order, yes that would be correct.

MS. RADWAY: So I have the next question. What are the types of costs that a business should expect to incur in the application submission process, and there additional yearly fees?

Maybe we can get some of our industry representatives to answer this question, as they would likely have experience in this.

MR. OGDEN: Oh, if I understood your question, it's what are the costs?

MS. RADWAY: Yeah.

MR. OGDEN: They're substantial. I think, and I've spoken on this in recent months as well. I mean, in various proposed rules, there are projections for what the cost to industry may be.

I've offered a number, that those numbers are 10X too low. I think for a -- in my view, for a proper and complete PMJ submission on an ENDS product, or at least a suite or a family

of products, I think you're talking I would say generically in the five to ten million dollar price tag range minimum. Depending on the types and durations of studies that you do, you could well be north of that.

MR. BURD: Okay. So I would start with the costs are probably going to come down. That's the good news over the next couple of years. But to start with, they're going to be substantial. I think with our company, most of our clients are into the several million for the application, and then what we tell them is once, you know, it's hard enough to get to that May 2020 date.

But then after that, if there's any additional information required, you need to pull that quickly. So at this stage it's very difficult as well because of a lack of resources, especially on the -- not necessarily on the lab testing side. I think we're finding some good support by companies like Enthalpy and a few out there.

But I think on the CRO side, it's going to be challenging to find those finite resources especially as we come down to the next -- we're less than six months now. Yeah, I think we're less than six months, so yeah.

MS. RADWAY: Any additional comments on that? Okay. We have a few more TPMF questions. Do you re-review items in the TPMF every time it's referenced, since it could be a different context each time?

MS. STARK: So this goes to an earlier point, where it's helpful to use some of the same content in TPF cross-multiple application types. The quick answer is we are going to be reviewing the TPMF when it is referenced by that submission. So let's take the earlier example of a non-clinical study, and let's state that that non-clinical study is being used to support a PMTA, and about six months or two months later it's being used to support a substantial equivalence report.

We will look at that content slightly

different depending on what the need is. So if we're looking in the SE report where it's being referenced, and let's just say that the differences are quite small, where we don't really have any issues around some of the ingredient changes, maybe we're not going to look at that non-clinical study as robustly as we would review it for the PMTA, where we're looking across different comparators within that product category or subcategory within the U.S.

So quick question is yes, we do take a peek for each application. When you're talking about efficiency though, because you're thinking gee, FDA you're going to be re-reviewing my material multiple times, we are going to be looking at what the reviewers cited and how they did the review for each application and see if it applies.

So in the case if you're looking at a PMTA and you're looking at a PMTA for a different product, we may be able to use those findings, look to see have we had additional amendments

come in that change our viewpoint or our findings, and then document our reviews with that. So there are some efficiencies gained as well on the FDA side with tobacco product master files, even if it's across application types. But it's going to be case-specific for how it's referenced.

MS. RADWAY: Did you have a comment? No. Can you put an entire application in a TPMF?

MS. STARK: That's a new one. I'm going to actually echo something Dr. Ogden just said. He just said why? When you submit an application, we're looking at -- and you look at the chart where we gave you a recommendation for what would facilitate our review with your common technical document, your first -- at the top of the pyramid that Ms. Allard presented was your administrative information.

Maybe that sounds great in a master file if you don't want to pre-populate that, but I'm going to just echo if you did it electronically, it's already there, so you

wouldn't have to retype it anyways. We're going to want to assign that submission tracking number anyways for that group set of products, and you're going to have other things that are specific to a PMTA.

So for example, samples. Samples do not belong under a Tobacco Product Master File. What's going to happen through the PMTA process is if the agency decides that samples are needed for verification of the content in the application, you're going to get a sample request letter. That's part of the PMTA. So we do not want to see your samples coming in here at headquarters with that master file. We'll give you a name and address and location for where those samples are sent.

So just some ideas to consider when you're looking at this. I want to just put a big note out. Look at electronic submissions, save them because you don't have to retype with those. If you're looking at using a study or a manufacturing process disclosure information for

multiple products, maybe that's where you consider your Tobacco Product Master File and then you have the two submissions where they interplay.

And again, we will take your comments and feedback so that we can discuss what is the best way for us to do this electronically, rather than having anyone physically drive it to our headquarters or submit electronic media in physical format.

MR. OGDEN: May I ask a follow-up question?

MS. RADWAY: Go ahead.

MR. OGDEN: I was trying to figure out a way to weave this in, and Cristi you just opened the door. So I heard Ms. Allard say that -- I believe what I heard her say this morning was that the PMTA submission would not be complete until FDA receives at least one sample, and then there may be a request for additional samples.

So the simple question is on

submission, should we automatically include one sample, or should we just wait for the request letter?

MS. STARK: So thank you for that, and this actually goes back to some of the content changing over time as we evolve with our programs. So in Ms. Busta's presentation, she had noted the one sample. In the past for PMTAs, that's what we had asked for. To facilitate both manufacturers and FDA, we are going to be -- when we review PMTAs, asking for an appropriate number of samples at that point in time and a manufacturer will receive a letter requesting it, with a physical address for samples to be shipped to, any time frame for when they need to be received.

It does not make sense for one sample to be sent, because you have to store one sample and you really can't test one sample. We do everything in replicates that we can see it. So that is a new clarification I'd like to put out there. Do not send one sample with your PMTA.

Instead, wait to see if FDA is going to ask for samples. The filing criteria for PMTA is samples as the Secretary may require.

So in some cases that may mean we are not asking for samples for every product. We'll be looking for what we need to verify the contents of the application. Does that help? Does it make more sense? Great.

MR. BURD: Yeah, just a quick note. I think one of the earlier presentations, the clock starts when the application and the sample is received?

MS. STARK: So the clock for PMTA starts when we have a complete application. So that can be one of two options. If samples are required for filing, it will be when we receive the application at our headquarters, hopefully submitted electronically through the CTP Portal, because that's open 24-7 and that's very helpful when there's a holiday or a weekend, and it's going to be when we receive the sample.

So for example, we have requested some

samples to be sent to our Southern Tobacco Laboratory. So the lab will verify that they have received every sample that's requested in the letter. In the case for a PMTA where an applicant does not receive a sample request letter, the start date for the application is when it's complete. So when the application has been received through our DCC.

Which is why it's helpful to know if you're getting samples or not. In general if you look, with the proposed rule FDA has proposed that samples are to be received within 30 days of receipt of that application. When we're looking at time frames, the goal for FDA is to quickly make a decision that it contains all required elements for acceptance, and then right after that surely issue a samples request letter if we're going to be asking for that.

If there are questions from a manufacturer, if samples are going to be required or the status of the application, please call that assigned RHPM. Their name, number and email

is listed at the bottom of the letter. They will be able to answer that question or quickly get back to you with that.

MS. RADWAY: Okay, thank you. I'm going to ask one more question and then we'll take a break. "Will the major amendment concept be applied across pathways, for instance, for a response to a deficiency letter on an SE report?"

MS. STARK: So like children, all of our pathways are special. I say this because I have kids and my teens and pre-teens are special, with all of the new problems that they bring home. PMTA is specific with its time frames. The statute provides that FDA will provide a decision within 180 days.

So the 180 days is coming from when we have a complete application. As we discussed earlier, if there is substantial information the agency has not previously reviewed that they must review, we are treating that as a new application, which is why that clock is reset for a new 180 days.

If you are looking at the substantial equivalence program, you're going to see it's a different time frame and we operate in cycles. So when you look in the statute under Section 905(j)(1)(A)(i), you're going to see that you should be submitting that 90 days prior to anticipated delivery or introduction for delivery into interstate commerce for commercial marketing.

That is our 90 day cycle. What happens at the end of that is you would either receive an order letter or a deficiency letter. That would close out that cycle and essentially when an applicant responds to that deficiency letter, a new 90 day cycle would start. So I'm just noticing differences in how the pathways are carved out.

The last pathway for marketing a new tobacco product is your exemption request. This is the exemption from substantial equivalence requirements. That's under 905(j)(3). With that one when we're looking at additives, it is

actually a more abbreviated version of what would go in an SE report, because you're only focused on your tobacco additives.

For that, FDA has placed out performance goals for statutorily regulated products for 60 days. We'll be treating it similar to the SE program, where at the end of 60 days from receipt of that application that would end and you would receive a deficiency letter. You would see that environmental information request letter for precluding everything for environmental considerations or that order letter. So all three are slightly different, but essentially what you're looking at here is you have a 60-day time frame for your exemption request and 90-day time frame for your SE regular reports. For your provisionals it's 120 days, and then you have a 180 days for your PMTAs.

All of that is for statutorily regulated. We do not yet have performance goals for deemed tobacco products. I know that is the next logical question. We are not prepared at

this point to issue any type of performance goals. We're going to want some experience working with industry, seeing what is needed for review and the time lines.

Similar to the SE program, we'd like to have a little bit of time in before we start to commit to any of that.

MS. RADWAY: Okay, thank you to all our panelists. We do still have some questions that we didn't get to for this panel, even though we went over a little bit on time. But I am going to save these questions for tomorrow's CTP leadership panel. So if you -- you can continue to submit your questions, but we'll take a break now for 15 minutes, so be back at 2:17. Thank you.

(Applause.)

(Whereupon, the above-entitled matter went off the record at 2:03 p.m. and resumed at 2:18 p.m.)

MS. RADWAY: Okay. I just want to give another thank you to all our panelists for

this afternoon. We'll now move on to the first set of presentations in Session 3, PMTA Scientific Content. First we have Ms. Ouida Holmes and Dr. Priscilla Callahan-Lyon presenting an overview of the PMTA content. Ms. Holmes?

MS. HOLMES: Good afternoon. My name is Ouida Holmes, and I am the program analyst in the Office of Science Division of Individual Health Science. Earlier today, Ms. Busta described the PMTA process with the focus on the programmatic aspects. My presentation will focus on scientific content. I will not review the bullet points as Emily did; however, it is important for applicants to ensure the PMTA addresses each of these points adequately, as they relate to Section 910 of the Tobacco Control Act.

With respect to PMTAs, to understand if a new tobacco product is appropriate for the protection of public health, which will now be referred to as APPH, FDA must evaluate a product's impact on the population as a whole,

meaning current tobacco product users as well as non-users.

Current tobacco product users are a broad category. Each of these types of tobacco product users may have varying health risks. As such, it is important for applicants to define populations especially in the context of study design. As an example, let's consider non-users. Non-users may be individuals who have not previously used tobacco products, but who are now experimenting or have never used a tobacco product.

In September of this year, FDA issued a proposed rule. The proposed rule is open for comment and closes on November 25th. If finalized the proposed rule will provide the general procedures for review from application receipt to order issuance, required manufacturers to maintain records establishing their tobacco products are legally marketed, and would help to ensure their applications contain sufficient information for FDA to determine whether to issue

a marketing order.

The proposed rule also describes the 180 day review clock, and explains when the clock can be paused or extended, when FDA can refuse to file applications, explain the different types of applications, allow applicants to cross-reference an existing application, describes how scientific literature or bridging can be used, and identifies post-marketing reporting requirements.

FDA is inviting comments on a number of issues including the topics, specific design parameters, how co-packaging products impact consumer use and behavior, definitions of commercially marketed and test marketing, required and requested information for marketing plans and the length of time it takes a tobacco product user to consume a single unit of a product.

After the comment period closes, FDA will review the comments and then determine next steps. Please note that the final rule may be different from the proposed rule. Comments to

the proposed rule can be submitted electronically to the website listed here or mailed.

In addition to the proposed rule, FDA has a PMTA ENDS guidance available that is relevant to PMTA submissions. The guidance is not FDA implemented policy; rather, the guidance communicates FDA's recommendations for submitting a PMTA as well as the general procedures by which FDA intends to review a PMTA.

A question an applicant may have is what is the difference between the PMTA proposed rule and the PMTA ENDS guidance? The difference between the PMTA proposed rule and the PMTA ENDS guidance is that the proposed rule is an official document that announces and explains the agency's plan to address content, format, review of a PMTA generally for tobacco products.

The PMTA for ENDS guidance was published to further clarify and assist in the review of ENDS tobacco products. A final guidance is not binding on the FDA or the public. However, it represents FDA's current thinking on

a topic. So let's move on to talking about various scientific studies and analysis that are helpful to support a PMTA.

First, it is important for the FDA to understand what the proposed product is and how it works. To understand what the product is, information relating to the product parts is useful, what it is made from and how it is manufactured. The chemistry evaluation takes into consideration information such as product formulation, chemistry design, tobacco blend, ingredients other than tobacco, manufacturing steps and controls, performance criteria, stability, ranges of exposure and aerosol content.

The engineering and microbiology analysis involves looking at product design, principles of operation as well as manufacturing and packaging. FDA currently does not have requirements on reporting of design features regarding specific products such as ENDS.

The proposed rule on PMTA state the

following information is helpful to assess the non-clinical risk of a new tobacco product such as identification of potential human health risk, focuses on exposures to users, describes packaging that may mitigate risk of accidental exposures to e-liquids, evaluation of ingredients including leachables and extractables. In addition, a list of useful considerations to include is described here.

The proposed rule on PMTA state that a PMTA include a comparison of the new tobacco product to a representative sample of a tobacco product legally on the market. When discussing comparator products information, it is important to have justification in your PMTA regarding why using data from certain other products to support your PMTA is appropriate.

The tobacco product market can be considered in many ways. The most appropriate comparators are likely to be what potential users of your proposed product already uses. For example for ENDS, manufacturers typically state

that the target consumer is a current smoker. Thus, cigarettes could be an appropriate comparator. It could also be appropriate for ENDS manufacturers to compare their products to similar other ENDS products.

The proposed rule states that applicants consider including the following information to assess the human health impact of a new tobacco product. Evaluations of the likelihood of initiation and cessation by both users and non-users of tobacco products may include evaluation perceptions of product risk, both absolute and in comparison to other tobacco products, as well as quitting all tobacco use, abuse liability and addictiveness, evaluation of product use patterns, evaluations of acute and longer-term health effects.

The applicant may use biomarkers of harm, biomarkers of exposure, health outcome measurements or other end points, labeling comprehension and human factor issues impacting product use and misuse. The proposed rule states

that each clinical investigation included in the PMTA should have been reviewed and improved by an Institutional Review Board.

Examples of human studies include likelihood of initiation and cessation studies, which can be defined in different ways. It is useful if clear definitions and rationale are provided for how they are being defined in any particular setting, in order to support meaningful interpretation of research findings. FDA acknowledges that it may not be feasible to directly measure the rate of uptake of a new product in the population if it has never been on the market.

Even if a product is on the market, there may not be a sufficient number of users to directly study initiation in an observational study. However, there are many different types of studies and lines of evidence that could provide information about the likelihood that the existing users will stop or non-users will start using tobacco products.

General principles suggest that multiple lines of evidence would strengthen an argument related to the likelihood of tobacco product initiation and cessation.

Moving on to human studies, I would like to start this section by discussing consumer perception studies. Understanding health risk of a product can be informed by evaluating the perception and appeal of a product and its impact on behavior intentions and actual behavior. Product perception intentions including how consumers, especially youth, perceive, use or intend to use the products is useful information to the FDA.

Qualitative research provides insights to individual's thoughts, feelings, behaviors and can serve as useful evidence in understanding a product's impact once it is on the market. Studies of consumer perception generally follow established methods such as the use of best practices for questionnaire design, to avoid bias and to ensure that the data collected is valid.

In addition, the sample size in these types of studies can vary depending on the research question, but usually a clear rationale for the sample size is given based upon practical considerations, statistical power to detect effects and other factors. The use of validated items whenever possible allows for the data collected to be compared to other studies, and also ensures that the data collected are measured for what they are intending to measure.

Along those lines, clearly defined aims that are specified before data collection begins allows for transparency. Overall, a clear explanation of the method and sample included in the study allows others to better understand the results and context. As in all human studies, protection of human subjects is a critical element and should be considered and described.

Information allowing FDA to evaluate how the proposed new product may influence initiation among youth is useful to determine the protection of public health. FDA does not

require youth behavioral studies at this time. However, information to allow FDA to evaluate how the proposed new product may influence tobacco initiation among youth is useful to determine if the product is APPH.

FDA will look to identify steps manufacturers took to minimize the risk to kids. Inferences regarding youth may be extrapolated from young adults, as well as derived from marketing data, scientific literature reviews, national surveys and/or bridging information.

Abuse liability testing is another type of assessment that may offer data and information to support an understanding of the likelihood of initiation and cessation of tobacco products. Abuse liability assessments traditionally are designed to evaluate the likelihood of abuse, which can also assess consequences of abuse. In general, the determination of a product's abuse potential can be accomplished through multiple lines of evidence.

Study design information that is helpful for FDA in reviewing pharmacology studies include comparison of nicotine's effects on pharmacodynamic PK and PD, switching studies, explanation of selection of prescribed puffing regimens, rationale for selection for comparator products, study limitations are identified and discussion of existing literature.

So let's move on to discuss product labeling. In order to authorize a PMTA, the proposed labeling cannot be false or misleading. A label comprehension study can be conducted to evaluate whether consumers understand the key label messaging and communication of information. The general design concepts to consider are to establish primary communication objectives, specify study designs that meets objectives and calculate appropriate sample size, enroll an appropriate population, construct a questionnaire that targets objectives, set priority target thresholds and using test labeling as close as possible to your final labeling is the most

useful.

Going back to thinking about the proposed product itself, human factors are important to consider when designing a product. Human factor considerations assess if users will be able to operate their product appropriately by focusing on the interactions between the people and products. Importantly, when considering a new proposed product, FDA seeks to understand the likely impact on human health.

To evaluate the acute and chronic health effects associated with the product or polytobacco product use, the proposed rule out for public comment states that the applicant include studies, other scientific evidence or both that identify biomarkers and health outcome measurements or end points, and provide data to support the impact of the new tobacco product on the health of users and non-users.

This may include health effects associated or related to specific constituents. When designing studies, it is helpful if the

study findings are generalizable to the population of U.S. users and non-users of your new tobacco product. If you are relying on published reports to support your PMTA, consider justifying why the data from those reports can be bridged to your product and are appropriate for determining the impact of the new product on the U.S. population that are likely the consumers.

In terms of individual risk, we are seeking to understand the product health impact on users and non-users. Clinical end points are the gold standard of understanding the impact of a product on health. However, clinical end points can take years to decades to develop. Appropriate biomarkers may serve as substitute end points and have the potential to correctly predict clinically meaningful end points in the interim.

Applicants have also asked what biomarkers are used to measure when evaluating tobacco products such as ENDS? As with all biomarkers, those that are specific to exposure

and have changes that are clinically relevant are the most useful. There is not an agreed upon panel of biomarkers established to understand ENDS impact on human health at this time.

Applicants have also asked what studies are required to support a PMTA? It may be possible to support a marketing order for a ENDS product without conducting new, non-clinical or clinical studies given other data sources can support this PMTA. In most situations, it is likely that at least some analytical testing specific to the product would be conducted to support your PMTA.

If conducting studies, alternatives to the traditional randomized, controlled clinical trials, which are typically used for drug development, may be appropriate to support a PMTA. Again, the most useful studies are those that are generalizable to the U.S. population.

If you have a product currently available on the market, it is possible that research has been done on that product or your

product is similar to other products which are the subject of publicly available research studies, in which case you may submit the available information along with bridging information to justify use.

Ideally, a PMTA will contain studies conducted with respect to the new tobacco product itself. But the bridging of data from different product to the new product that is subject of the application may be feasible for a subset of products or for certain types of studies. It is likely that most PMTAs will include various data sources to support the submission such as published or peer-reviewed literature, analysis of existing national data sets such as NYTS or PATH, and original scientific investigations.

Literature reviews are a likely component of PMTAs, as I just mentioned, and literature reviews typically include the purpose of the review, the evaluation of methods, the review of results, bibliography and conducting independent analysis of published studies that

include study details can also support a PMTA.

Finally, moving on to what is APPH in the FDA PMTA review. I have reiterated that FDA must determine if the proposed product, which is subject of the PMTA, is APPH. Applicants must address the statutory requirements as appropriate pertaining to PMTAs in the Act. All ingredients, components, constituents are evaluated based upon how they contribute directly and indirectly to the total health impact of a specific product.

To facilitate review, it is important to summarize the key product characteristics and study results that you believe would make the marketing of your product APPH. The questions listed on this slide are examples of the types of issues FDA has discussed in deciding whether a product is APPH.

Are HPHCs and other toxic constituent levels in the new tobacco product similar or lower than levels of other appropriate comparator products? Does the scientific evidence indicate lower disease risk to an individual compared to

the appropriate comparator? Will the marketing of a new tobacco product affect the likelihood of non-user uptake, cessation rates or other significant shifts in user demographics in a manner to decrease morbidity and mortality from tobacco product use?

It is the applicant's responsibility to provide scientific evidence and justification to support that a product is APPH. A product that is found APPH today may not be APPH in the future.

In the next few slides, I will talk about the challenges FDA has in reviewing PMTAs. Here are some examples of challenges seen by FDA reviewers during the acceptance review. Applications have been sent to FDA without including an environmental assessment. Applications have been sent in a format that FDA cannot process, and applicants have sent in information with insufficient product identifying information.

FDA reviewers have also identified

incomplete or missing information on the following items during the scientific review phase: ingredients, product stability testing, design parameters, manufacturing steps, manufacturing facilities, some of the facilities in the application are listed but not all of them are described, study design and reports are not included even though a study may have been mentioned, and biomarkers may have been evaluated but there is no rationale for the selection of biomarkers used and the results were not interpreted.

In addition, a mission of protocols and methodology validation reports, missing data from clinical and non-clinical studies, studies submitted were conducted on a prototype of the device and not the device actually subject for marketing, and bridging data was not provided to clearly link the information. It can be difficult to distinguish which version of the product is intended for market, and deciphering tobacco product naming conventions can also be

problematic.

Another significant challenge that impedes progress is the applicants have sent new study data and large amendments to FDA for review towards the end of FDA's scientific review phase. Reviewing additional information has caused delays in FDA issuing marketing/no marketing orders.

I've discussed a lot of information in a short amount of time. I hope that you've found the information helpful in your effort to develop a quality PMTA submission. Up next is my colleague Dr. Callahan-Lyon. She will provide in her presentation examples of informative studies and other supportive information from the IQOS submission. Thank you for your time.

(Applause.)

DR. CALLAHAN-LYON: Hi, good afternoon. I'm Priscilla Callahan. I'm the deputy director for the Division of Individual Health in FDA's -- oh sorry. I'll start over.

I'm Priscilla Callahan. I'm deputy

division director in Division of Individual Health Sciences, CTP's Office of Science. I'm going to discuss some information regards to the IQOS submission and specifically what kinds of information they used in that submission that allowed us to authorize marketing of the product as a PMTA.

So just for those that may not know, IQOS is a non-combustion cigarette product. It includes a HeatStick, a holder and a charger. The tobacco is heated with this product. It's not burned or combusted, and I've included a picture of the device and the holder and the HeatStick packaging here.

So what types of information did they include in their applications? I'm going to go through this at a very high level, keeping in mind the kinds of things that Ms. Holmes just discussed in her PMTA presentation. I also have included on some of the slides just you'll see a note in a red circle, just hints and other suggestions that you might consider in your PMTA

applications for the future.

So with regards to engineering data, they provided us a complete description of the product designs and parameters, as well as manufacturing steps and quality control measures. They also outlined very clearly the process, controls and quality assurance measures to ensure that the products met manufacturing specifications that were set by the applicant, and that they would be manufactured in a consistent manner.

There was performance standards and performance testing to verify product design, and specifications and independent test results for the battery were conducted by FDA and found to be satisfactory.

With regards to chemistry, they provided a complete list of the uniquely identified components, ingredients and additives with applicable specifications and a description of the intended function of each of these materials, as well as a description of the steps

and the quality control measures, and evidence of product stability including microbiological testing.

The testing data for certain HPHCs was included in the applications. These are some of the ones that were included. But I have from a note here "Applicants should provide data that will assist FDA in determining their product is APPH and the specific types of information needed may vary, depending upon the product type.

With regards to the toxicological risk assessment, the applications included measures of HPHCs in the aerosols and compared it to 3R4F cigarette smoke. They also made comparisons for HPHCs and tar to U.S.-marketed cigarettes. They included measures of nicotine in the HeatSticks and the aerosol, as well as non-targeted differential screening assays, and in vitro and in vivo studies.

For the behavior and clinical pharmacological assessment, four PK/PD studies were included in the applications. There were

also four exposure studies, two of which lasted for five days and two of which lasted for 90 days, and one actual use study. Another note: information to consider may include nicotine exposure relative to other tobacco products, abuse liability, the attractiveness and likeability of your product, and the likelihood of switching and/or use of multiple products.

For individual health impact, they included quite a lot of information. We had the four exposure studies that were mentioned earlier, and these did include measures of biomarkers of exposure. The biomarkers of exposure were selected by the applicant to correspond with 14 HPHCs and nicotine and nicotine alkaloids.

They were assessed after a five day confinement period and also after a 90-day ambulatory period and compared results were given for studies conducted in the United States and in other countries where the product is currently marketed.

As regards to biomarkers of potential harm, they selected these and these were also selected by the applicant on the basis of key mechanisms for three smoking-associated diseases, cardiovascular disease, COPD and lung cancer. The applicant selected these and provided the rationale as well as significant literature on the selected BOPHs and the relationship with the diseases of interest.

Other individual health impact measures included adverse experiences associated with the acute exposure in the clinical studies, an actual use study to evaluate uptake and use in the current U.S. adult cigarette smokers, consumer reports and complaints from countries where their product is currently marketed, an updated literature review during the course of the application review with case studies and other reports, and they also provided long term six month continuation of one clinical study, with long-term BOE and BOPH data, and information on uptake, continued use and dual use.

Not all of these may be needed for any particular product application, so what you need to consider is what information FDA needs in order to determine that marketing of the product is APPH and how it can best be provided.

With regards to other factors under individual health, we consider the human factors. This was discussed to some degree by Ms. Holmes. This is the way people will actually use the product, an actual use study to assess product misuse, as well as an evaluation of the advanced device malfunctions and other potential for serious issues.

The applicant also included consumer comprehension study of the labeling and what they did with this was by a study evaluating the ability of prospective customers to understand and comply with product instructions. This is another note.

The type of human factor studies and comprehension testing may vary, depending on the product type and the potential for misuse, and

may also be important to demonstrate that the product is unlikely to expose high risk groups such as children.

With regards to population health, we have to consider several things and you've heard these today. Number one is the likelihood of product use by current cigarette smokers, so in this particular application they included a perception study with different brochures with package labeling and warning statements, and the study included smokers, former smokers, never smokers and young adult never smokers.

Information was also submitted with the actual use study, which evaluated use of the product in the United States, and included product initiation and use patterns as well as dual use and switching over a period of six weeks. Whole offer testing was their term for a product study that was conducted outside of the United States, and evaluated product initiation and use patterns in other countries where the product was already currently marketed.

With regards to polyuse of the product with cigarettes or other tobacco products, the applicant provided data from two different post-marketing surveys in a country where the product is already marketed, as well as additional data from the actual use study and the clinical studies.

With regards to the likelihood of the use of the product leading to cigarette smoking cessation, again we had information from the actual use study and the whole offer test, as well as post-market survey information. Other population health impact studies that were included were uptake of the product by former and never smokers or youth. This is obviously of great interest to FDA.

So the perception study did provide some information with regards to the intent to try the product in former smokers, never smokers and young adult smokers or never smokers. The cross-sectional studies were also conducted to monitor prevalence of this in similar products in

adult non-smokers. There was some data from outside of the United States where the product is currently marketed, as well as face to face survey data that were presented from a different country, where participants as young as 15 years old were surveyed on their likelihood of use of the product.

Of note, there was no specific U.S. data provided for youth. In this particular situation, FDA must consider the likelihood that those not using the tobacco product will start using the product, and although youth studies are not specifically required, we do need you to consider how the information that you can provide will be used to support this particular aspect of FDA review.

Marketing plans were included in the applications. These were very high level and provided a general approach to their marketing strategy with sample labeling. They also clarified at our request their strategy for limiting youth exposure and hopefully uptake of

the products.

In addition, in the post-marketing reporting period, which was included in the marketing authorization letter, we provided requirements for them to provide FDA with periodic reports of product sales and distribution by location, market type and product type. We also included the situation where they will provide prior notification to FDA for marketing plans and materials.

They will provide an analysis of delivery of advertising impressions by age breakouts. Adverse health reports will be included in period reporting, as well as other consumer complaints, especially those regarding product quality.

So in summary, I'm going to go back to some of the points that have been made before, it is very, very important that you include all of the information in your original submission. As has been mentioned several times, amendments are challenging. Each amendment must be evaluated as

to whether it's major or minor, and major amendments can prolong your product review and delay a decision.

The other point I want to make is that it's important to provide FDA a very clear picture that we can follow during the application review, using consistent terminology such as product naming, study name, consistently throughout the application makes it very helpful and is much easier for us.

Organizing the data and provide an accurate table of contents with all the codes and definitions and other materials that we need in order to review the applications. If you're bridging data, provide a rationale and clear explanation for why this is important for your particular product, and clearly describe your approach, the study methods, the approach to the statistical analysis, the literature search methods and terms and anything else that you think would make it easier for us to review your applications. Thank you.

(Applause.)

MS. RADWAY: Thank you again to Ms. Holmes and Dr. Callahan-Lyon. Next, we will have Ms. Christine Saba discussing PMTA Post-Marketing Requirements.

MS. SABA: Okay. I believe I'm the last presentation of the day, and so I will try and keep my remarks brief, to get everybody out of here on time. Today, I will be presenting the proposed premarket tobacco product application post-market reporting requirements for industry.

On September 25th, 2019, FDA gave notice of a proposed premarket tobacco applications and recordkeeping requirements rule, the PMTA NPRM. This proposed rule is available and open for public comment through November 25th, 2019. This presentation will review post-market reporting requirements outlined within the PMTA NPRM. Note these are subject to change within the final rule.

PMTA NPRM Subpart D outlines the proposed post-market reporting requirements.

Applicants would be required under this proposed section to submit two types of report to FDA after receiving a marketing order, periodic report and adverse experience reports.

Applicants would need to submit periodic reports within 60 calendar days of the reporting date specified within the marketing order. Adverse experience reports would be required to be reported to FDA within 15 calendar days of receipt or identification. It is proposed that the report include the following: A cover letter that contains the PMTA STN, tobacco product name or names, the company name, date of report and the reporting period.

The proposed rule states that each post-market report must be well-organized, legible and written in English. Documents that have been translated from another language into English such as original study documents written in a language other than English must be accompanied by the original language of the study documents, as well as a signed certificate from

the manufacturer certifying that the English language translation is complete and accurate.

As mentioned, the PMTA NPRM proposes two types of reports that an applicant would be required to submit following a marketing order, periodic reports and adverse experience reports. FDA anticipates that periodic reports would be required on an annual basis, but FDA may require in a specific order that reports may be made more or less frequently, depending on a number of factors such as the novelty of the type of product.

This slide presents a high level overview of the proposed data elements for each report. Adverse experience reports would include reporting of serious adverse experiences such as death, life-threatening event, inpatient hospitalization, incapacitation of user, birth defect, any other adverse or serious condition affecting quality of life, as well as unexpected adverse experiences.

Each of these would be required to be

reported to FDA within 15 calendar days of receipt or identification. Periodic reports include the following broad proposed data categories: a description of the changes made to the manufacturing facilities or controls that do not modify the finished tobacco product, inventory of ongoing and completed studies of the tobacco product, a summary of sales and distribution data, data on current product purchasers, final labeling specimens and labeling changes, marketing and advertising implementation plans and reports. These reports will be discussed in more detail in the upcoming slides.

First, we will cover adverse experience reporting. The PMTA NPRM proposes the applicant report all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or that the applicant is aware of to CTP's Office of Science through the HHS Safety Reporting Portal within 15 calendar days after the report is received by the applicant.

Qualifying serious adverse experiences were listed in the previous slide, so I won't repeat them again. Unexpected adverse experiences would also be required to be reported. FDA's proposed definition for unexpected adverse experience can be found in Subpart A of the PMTA NPRM. This reporting also includes manufacturing deviations.

For products that have been distributed, if a deviation occurs that presents a reasonable probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in tobacco products on the market that could cause serious adverse health consequences or death, the applicant would be required to report this deviation to FDA within 15 calendar days of identification.

Now we'll cover periodic reporting in more detail. The PMTA NPRM proposed periodic reporting requirements for manufacturing changes, deviations and adverse experiences include a summary and analysis of serious and unexpected

adverse experiences identified during the reporting period, accompanied by a statement of any changes to the overall risk associated with the tobacco product and a summary of any changes in the health risks, including the nature and frequency of the adverse experience, as well as potential risk factors.

It should include a summary of all manufacturing deviations, including those associated with the processing, testing, packaging, labeling, storage, holding and distribution. Note that serious adverse experiences and manufacturing deviations that may cause serious adverse health consequences should be reported to FDA twice through the safety reporting portal as events are initially received and again for periodic reporting.

A summary of changes made to the manufacturing facilities or controls that do not modify the finished tobacco product such as manufacturing process changes compared to what was submitted into the PMTA should also be

reported, as well as a rationale for each change. FDA issues marketing orders for the specific new tobacco product described within the PMTA. An applicant may not make any modification including a 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 to the product that is the subject of the order.

Any modification to the tobacco product that would result in a new tobacco product under the definition in Section 910(a)(1) of the FD&C Act would require the applicant to submit a new tobacco product application for the modified tobacco product.

Changes that do not result in a new tobacco product, such as manufacturing product changes that do not modify the finished product would be required to be reported under periodic reporting as described in Subpart D of the PMTA NPRM.

FDA may notify an applicant that FDA

has determined that a change described in a periodic report results in a new tobacco product outside the scope of the marketing order, requiring the submission of a new tobacco product application and issuance of a new marketing order if the applicant seeks to market the new tobacco product, unless that tobacco product can be legally marketed through a different premarket pathway.

Applicants seeking to make modifications to the tobacco product authorized under a standing order may submit a standard PMTA, a supplemental PMTA or request for an exemption from substantial equivalence for the modified product in order to seek marketing authorization for that new product.

Supplemental PMTAs are based on a cross-referencing system to reduce the burden of both preparing and reviewing a PMTA. Note that the applicant may not market the new tobacco product unless FDA has authorized its marketing. Failure to do so would render it adulterated

under Section 910(f) of the FD&C Act, and would be subject to enforcement action.

The PMTA NPRM proposes the applicant report the following: an inventory of all ongoing and completed studies about the tobacco product conducted by or on behalf of the applicant that were not already submitted as part of the PMTA or previous post-market reports.

Full reports of information published or known to or which should be reasonably known to the applicant concerning scientific investigations and/or literature about the tobacco product that were not previously submitted as part of the PMTA or previous post-market reports, as well as significant findings from publications that have not been previously reported to FDA.

An assessment of how the product continues to be appropriate for the protection of public health would be required. When determining whether the marketing of a particular new tobacco product would be appropriate for the

protection of public health, FDA will evaluate the factors in light of available information regarding the existing tobacco product market, tobacco use behaviors and associated health risks at the time of review.

The PMTA NPRM proposes the reporting of a summary of sales and distribution data of the tobacco product to the extent that the applicant collects or receives such data for the reporting period including total U.S. sales reported in dollars; units and volume, with breakdowns by U.S. Census region, major retail markets and channels in which the product is sold; the universal product code or codes that correspond to the products or product identified in the PMTA; and demographic characteristics of product purchasers such as age, gender and tobacco use status.

Proposed requirements for labeling and advertising include specimens of all labeling and descriptions of all labeling changes that have not been previously submitted to FDA, including

the date the labeling was first disseminated and the date when dissemination was completely terminated, as well as full color copies of all advertising for the tobacco products that have not been previously submitted to FDA, as well as the date the materials were first disseminated and the date the dissemination was completely terminated.

The proposed reporting requirements for reporting marketing and advertising plans include a description of the implementation of all advertising and marketing plans by channel and by product, including a dollar amount of each such plan, including a description of any use of competent and reliable data sources, methodologies and technologies to establish, maintain and monitor highly targeted advertising and marketing plans and media buys; use of owned, earned, shared media, public relations outreach, paid social media, partners, influencers, bloggers or brand ambassadors to create labeling for, advertise, market or promote the products;

consumer engagements conducted by the applicant or on its behalf or at its direction, including events at which the products were demonstrated; as well as an analysis of actual delivery of advertising impressions including breakouts by age ranges to the extent that this is applicable.

Additional proposed reporting includes a description of any targeting of specific adult audiences by age range including young adults ages 18 to 24, and other demographic or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys, as well as actions taken to restrict youth access and limit youth exposure to the product's labeling, advertising, marketing or promotion.

PMTA NPRM proposed Section 1114.31(b) would allow FDA, using its authority under Section 910(f) of the FD&C Act, to require an applicant to submit post-market reports in addition to those described in PMTA NPRM Subpart

D, including but not limited to requirements that an applicant provide information such as labeling, advertising, marketing or promotional materials or marketing plans not previously submitted to FDA, and to do so at least 30 days prior to the initial publication, dissemination to consumers or use in engaging or communicating with consumers of such materials.

In conclusion, the data described in PMTA NPRM Subpart D are especially important for FDA to review, because the data inform the determination of whether or not the new product continues to be appropriate for the protection of public health. In particular, the data help FDA to assess whether the information regarding likely tobacco product use behavior described within the PMTA lines up with actual use of the product after authorization.

For example, if youth initiation rates associated with the new tobacco product are not what was anticipated within the PMTA, FDA may decide that the product is no longer appropriate

for the protection of public health and the marketing authorization may be withdrawn.

Finally, please note that PMTA NPRM is open for public comment until November 25th, 2019, although similar to other NPRMs the comment period for this may be extended. Applicants may review the IQOS marketing authorization as a reference for post-market reporting requirements, but exact requirements of a marketing order can vary. Thank you.

(Applause.)

MS. RADWAY: Thank you Ms. Saba. So this concludes our content for today. A special thank you to all the presenters and panelists, and all those submitting questions. As a reminder, tomorrow the room that we have will be much smaller, so keep that in mind, and we'll pick back up tomorrow on the next part of Session 3, starting with a presentation. Thank you.

(Applause.)

(Whereupon, the above-entitled matter went off the record at 3:08 p.m.)

C E R T I F I C A T E

This is to certify that the foregoing transcript

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Before: US FDA

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was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

/NEAL R. GROSS/

Court Reporter