

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

2 8:37 a.m.

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

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

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

1 that means in terms of application review.

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

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

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

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

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

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

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

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

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

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

22 While there might be various

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

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

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

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

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

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

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

1 (Applause.)

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

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

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

22 One other thing I wanted to mention is

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

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

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

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

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

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

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

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

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

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

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

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

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

1 updated pages, and also how to contact CTP.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Then the FDA considers comments and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 labeling and advertisements.

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

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

1 manufacturer-distributor and important compliance
2 information.

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

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

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

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

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

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

1 application. You can search on any keyword or
2 topic.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 for your attention and time.

2 (Applause.)

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

14 Ms. Allard?

15 MS. ALLARD: Thank you.

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

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

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

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

22 First, there will be a quiz. Don't

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

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

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

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

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

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

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

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

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

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

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

1 me in the photo too. I like it.

2 (Laughter.)

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

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

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

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

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

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

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

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

6 So here's the standard pyramid. This
7 is the basis of the information. The reason it's
8 put into a pyramid is because the majority of the
9 information that you would submit are in modules
10 3 through 7 down at the bottom. The middle
11 bucket is where you would put summaries that
12 summarize all that information.

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

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

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

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

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

22 You're going to hear about master

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

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

22 It also provides support for group

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

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

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

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

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

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

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

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

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

13 Module 4, this is where the non-
14 clinical information goes, right? So if you've
15 done non-clinical studies you can do a list of
16 all of those, your non-clinical studies, all of
17 the results. Behavioral studies for non-clinical
18 would also go here. You can include your non-
19 clinical literature reviews and any 904(a) or
20 904(b) information. Oh sorry, I misread that.
21 That's 911(d) and 910(b). I'm still learning the
22 regulations, I'm not going lie.

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

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

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

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

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

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

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

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

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

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

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

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

7 Working hypertext links and bookmarks.

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

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

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

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

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

22 This one is a little bit less

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

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

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

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

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

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

1 You can download the eSubmitter software.

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

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

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

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

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

11 (Show of hands.)

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

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

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

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

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

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

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

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

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

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

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

3 Include the full legal address of the
4 organization. Don't include a personal address.

5 We want the organization that you're requesting
6 the account on behalf of. That's what we care
7 about. Make sure the email address is correct.
8 That's really important. That's how we'll
9 communicate with you that your account's been
10 created. So you'll want to make sure it's
11 correct and then you'll want to monitor it pretty
12 regularly.

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

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

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

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

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

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

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

3 (Laughter.)

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

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

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

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

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

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

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

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

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

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

1 fine. Data. Data-driven decision-making.

2 (Laughter.)

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

8 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 MS. RADWAY: Thank you.

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

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

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

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

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

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

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

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

4 MS. RADWAY: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 individuals so some of these updates.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 DR. CAMPBELL: No issues here either.

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

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

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

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

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

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

1 may be helpful in the future.

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

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

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

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

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

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

22 MS. RADWAY: Are there --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MS. RADWAY: Okay, thank you. I guess

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

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

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

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

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

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

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

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

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

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

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

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

19 MS. RADWAY: Thank you.

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

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

7 MS. STARK: So I'll give one last
8 plug. I know that May 2020 is coming up and
9 people are very nervous. But I'm going to ask
10 that you don't wait. If you know that you need
11 to create an account and get an industry account
12 manager, do it now. Although it only takes 7 to
13 14 days to have that in place, that is when
14 everything is filled out and appropriate.

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

22 So I'm going to ask that you guys plan

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

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

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

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

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

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

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

11 (Applause.)

12 (Whereupon, the above-entitled matter
13 went off the record at 10:22 a.m. and resumed at
14 10:40 a.m.)

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

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

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

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

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

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

5 To introduce the PMTA pathway, I will
6 begin with the statutory requirements as
7 described in Section 910 of the Federal Food,
8 Drug, and Cosmetic Act. An order under Section
9 910(a)(2) is required to legally introduce and
10 market a new tobacco product in the United
11 States. The PMTA pathway has been considered the
12 primary pathway for a new tobacco product to come
13 to market.

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

1 appropriate.

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

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

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

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

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

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

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

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

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

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

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

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

22 In general, meetings should be held at

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

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

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

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

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

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

22 In the first column of this table, we

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

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

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

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

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

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

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

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

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

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

8 Some of these additional properties
9 for an e-liquid can be found in red on the table.
10 These may include, for example, e-liquid volume,
11 nicotine concentration, the ratio of propylene
12 glycol to vegetable glycerine, and additional
13 properties as necessary. Additional properties
14 will be added when the list of properties are not
15 sufficient to identify a tobacco product.

16 Additional properties necessary upon
17 identification may not be identified during
18 acceptance phase, but may be found during
19 substantive review.

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

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

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

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

22 The premarket tobacco product

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

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

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

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

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

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

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

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

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

1 should also be included.

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

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

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

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

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

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

22 The substantive review phase is a

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

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

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

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

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

7 CTP generally expects that when an
8 applicant submits a PMTA, the submission will
9 include all information required by Section
10 910(b)(1) of the FD&C Act. However, CTP
11 recognizes that additional information may be
12 needed to complete the review of a PMTA. If CTP
13 determines additional information is needed to
14 render a decision, the applicant will be notified
15 by letter and given a period of time by which
16 they will need to respond.

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

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

8 Because Section 910(c)(1) of the FD&C
9 Act requires FDA to issue an order for an
10 application meeting the requirements of Section
11 910(b)(1) within 180 days of its receipt, a new
12 180 day period will begin upon the receipt of a
13 major amendment. CTP generally does not intend
14 to review unsolicited amendments that would
15 require significant review time by the agency.
16 If the applicant submits information that is not
17 requested by CTP, this may be identified as an
18 unsolicited amendment and CTP is not obligated to
19 review the submission.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 Please note that the numbers presented
5 today are subject to change as they only reflect
6 application status through September 30th, 2019.
7 On this slide, I am showing some recent metrics
8 related to the PMTA program for statutorily
9 regulated products for fiscal year 2019. For
10 clarity, fiscal year 2019 runs from October 1st,
11 2018 to September 30th, 2019.

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

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

1 September 30th, 2019.

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

7 Now I'd like to shift our focus to
8 deemed tobacco products, as this is one of the
9 main points of this meeting. On this and the
10 following slide are some recent metrics for
11 deemed tobacco products in the PMTA pathway. We
12 have received 16 PMTAs for deemed products in the
13 2019 fiscal year. Of those 16, 15 are still open
14 in the review process with FDA and one is closed.

15 This slide captures cumulative metrics
16 for PMTAs received for deemed products. CTP has
17 received 389 PMTAs for deemed tobacco products.
18 Many of these were received prior to fiscal year
19 2019. Of these 389, 370 were closed. A large
20 number of these were closed due to a lack of
21 environmental assessment. It is important when
22 submitting an application that it contains all

1 required elements.

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

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

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

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

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

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

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

1 submission. As you may be aware, on September
2 25th, 2019, FDA issued a proposed rule to set
3 forth requirements related to the content, format
4 and review procedures for PMTAs as part of the
5 agency's continued commitment to its oversight of
6 e-cigarettes and other tobacco products.

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

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

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

16 Per the rulemaking process, once the
17 comment period for the proposed rule closes,
18 currently set to 60 days closing on November
19 25th, 2019, FDA will review and analyze the
20 comments and then determine the appropriate next
21 steps. CTP is inviting comments on the topic in
22 this proposed rule and we want to hear from you.

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

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

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

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

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

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

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

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

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

10 (Applause.)

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

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

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

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

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

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

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

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

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

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

1 ingredients and composition of the cherry e-
2 liquid.

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

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

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

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

8 For example, if a manufacturer,
9 Company C, utilizes the same ENDS device in 50
10 products, they could submit a TPF that utilizes
11 all of the manufacturing information for that
12 ENDS device. In lieu of reporting this
13 information in 50 premarket applications, Company
14 C could reference their own TPF.

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

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

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

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

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

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

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

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

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

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

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

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

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

5 The content of the TPMF may include
6 tobacco product information such as ingredients,
7 additives and constituents which can be housed in
8 Module 3.2, non-clinical behavioral studies,
9 which can be housed in Module 4.3, and abuse
10 liability studies, which can be housed in Module
11 5.2.

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

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

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

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

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

22 As mentioned a few slides earlier, CTP

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

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

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

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

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

13 If an owner is clarifying a section
14 with a significant amount of edits, it may be
15 helpful to resubmit the entire TPFM or the entire
16 section of the TPFM.

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

1 different submissions may have different
2 information content needs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 letters.

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

8 (Applause.)

9 MS. RADWAY: Thank you to both of our
10 presenters. Now we are going to break for lunch
11 a little bit early, and then we will still only
12 take one hour for lunch. So we'll be back at
13 12:40. Thank you.

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

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

1 discussions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 All versions of study materials, for

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

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

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

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

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

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

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

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

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

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

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

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

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

1 facility and equipment assessments.

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

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

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

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

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

12 (Applause.)

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

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

1 Mr. Burd, you can start.

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

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

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

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

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

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

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

1 guidance documents for method validation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 it a little bit.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MR. OGDEN: Since Cristi called on me,

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

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

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

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

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

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

17 MR. OGDEN: That was my answer.

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

21 (Laughter.)

22 MS. STARK: So let's talk about if

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

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

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

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

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

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

22 MS. RADWAY: Thank you. Okay, next

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

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

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

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

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

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

1 unauthorized at the time.

2 MS. RADWAY: Do you want to go?

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

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

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

1 the agency. There may be press releases.

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

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

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

1 aware through that process.

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

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

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

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

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

8 But in the case where we have the
9 deemed products that are already on the market,
10 with a deadline of May 12 for submission, it's
11 very analogous to the provisional SEs of March 21
12 of 2011. So in the current case, if an
13 application the way I look at it, if it's not
14 been submitted to the agency by May 12, on May 13
15 it is illegal. That is something that I think
16 FDA should take the leadership position in in how
17 to get that information to retailers, to
18 wholesalers, to the general public, to know --
19 and I know you can't do it in a day. But within
20 30 or 60 days, it seems like that would be
21 something that the agency should take the lead
22 on, is to make sure that those products are --

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

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

11 But they are under a compliance,
12 compliance policy right now until that May 12th,
13 2020. But the goal is that we would be providing
14 information as we are allowed, to the list of
15 products that are, haven't -- we have not
16 received applications for.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 information.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Through that process, we are going to

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

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

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

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

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

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

22 As we heard earlier, FDA may issue

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 enforces.

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

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

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

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

1 other tobacco products, or only ENDS?

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

11 MR. BURD: And just to clarify too,
12 you know, so that once the May deadline hits,
13 they have 12 months to complete that application
14 process. If there's maybe one or two or several
15 180-day extensions, you can only get two is my
16 guess, and then you're likely going to come up
17 against the May 2021. And if you come against
18 that date and are still not completed, then you
19 would need to come off the market; correct?

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

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

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

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

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

13 MS. RADWAY: Yeah.

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

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

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

6 MR. BURD: Okay. So I would start
7 with the costs are probably going to come down.
8 That's the good news over the next couple of
9 years. But to start with, they're going to be
10 substantial. I think with our company, most of
11 our clients are into the several million for the
12 application, and then what we tell them is once,
13 you know, it's hard enough to get to that May
14 2020 date.

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

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

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

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

22 We will look at that content slightly

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

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

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

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

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

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

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

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

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

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

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

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

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

13 MS. RADWAY: Go ahead.

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

22 So the simple question is on

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

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

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

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

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

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

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

22 So for example, we have requested some

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

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

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

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

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

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

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

1 If you are looking at the substantial
2 equivalence program, you're going to see it's a
3 different time frame and we operate in cycles.
4 So when you look in the statute under Section
5 905(j)(1)(A)(i), you're going to see that you
6 should be submitting that 90 days prior to
7 anticipated delivery or introduction for delivery
8 into interstate commerce for commercial
9 marketing.

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

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

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

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

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

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

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

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

17 (Applause.)

18 (Whereupon, the above-entitled matter
19 went off the record at 2:03 p.m. and resumed at
20 2:18 p.m.)

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

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

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

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

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

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

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

1 a marketing order.

2 The proposed rule also describes the
3 180 day review clock, and explains when the clock
4 can be paused or extended, when FDA can refuse to
5 file applications, explain the different types of
6 applications, allow applicants to cross-reference
7 an existing application, describes how scientific
8 literature or bridging can be used, and
9 identifies post-marketing reporting requirements.

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

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

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

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

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

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

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

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

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

22 The proposed rule on PMTA state the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 useful.

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

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

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

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

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

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

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

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

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

20 If you have a product currently
21 available on the market, it is possible that
22 research has been done on that product or your

1 product is similar to other products which are
2 the subject of publicly available research
3 studies, in which case you may submit the
4 available information along with bridging
5 information to justify use.

6 Ideally, a PMTA will contain studies
7 conducted with respect to the new tobacco product
8 itself. But the bridging of data from different
9 product to the new product that is subject of the
10 application may be feasible for a subset of
11 products or for certain types of studies. It is
12 likely that most PMTAs will include various data
13 sources to support the submission such as
14 published or peer-reviewed literature, analysis
15 of existing national data sets such as NYTS or
16 PATH, and original scientific investigations.

17 Literature reviews are a likely
18 component of PMTAs, as I just mentioned, and
19 literature reviews typically include the purpose
20 of the review, the evaluation of methods, the
21 review of results, bibliography and conducting
22 independent analysis of published studies that

1 include study details can also support a PMTA.

2 Finally, moving on to what is APPH in
3 the FDA PMTA review. I have reiterated that FDA
4 must determine if the proposed product, which is
5 subject of the PMTA, is APPH. Applicants must
6 address the statutory requirements as appropriate
7 pertaining to PMTAs in the Act. All ingredients,
8 components, constituents are evaluated based upon
9 how they contribute directly and indirectly to
10 the total health impact of a specific product.

11 To facilitate review, it is important
12 to summarize the key product characteristics and
13 study results that you believe would make the
14 marketing of your product APPH. The questions
15 listed on this slide are examples of the types of
16 issues FDA has discussed in deciding whether a
17 product is APPH.

18 Are HPHCs and other toxic constituent
19 levels in the new tobacco product similar or
20 lower than levels of other appropriate comparator
21 products? Does the scientific evidence indicate
22 lower disease risk to an individual compared to

1 the appropriate comparator? Will the marketing
2 of a new tobacco product affect the likelihood of
3 non-user uptake, cessation rates or other
4 significant shifts in user demographics in a
5 manner to decrease morbidity and mortality from
6 tobacco product use?

7 It is the applicant's responsibility
8 to provide scientific evidence and justification
9 to support that a product is APPH. A product
10 that is found APPH today may not be APPH in the
11 future.

12 In the next few slides, I will talk
13 about the challenges FDA has in reviewing PMTAs.
14 Here are some examples of challenges seen by FDA
15 reviewers during the acceptance review.
16 Applications have been sent to FDA without
17 including an environmental assessment.
18 Applications have been sent in a format that FDA
19 cannot process, and applicants have sent in
20 information with insufficient product identifying
21 information.

22 FDA reviewers have also identified

1 incomplete or missing information on the
2 following items during the scientific review
3 phase: ingredients, product stability testing,
4 design parameters, manufacturing steps,
5 manufacturing facilities, some of the facilities
6 in the application are listed but not all of them
7 are described, study design and reports are not
8 included even though a study may have been
9 mentioned, and biomarkers may have been evaluated
10 but there is no rationale for the selection of
11 biomarkers used and the results were not
12 interpreted.

13 In addition, a mission of protocols
14 and methodology validation reports, missing data
15 from clinical and non-clinical studies, studies
16 submitted were conducted on a prototype of the
17 device and not the device actually subject for
18 marketing, and bridging data was not provided to
19 clearly link the information. It can be
20 difficult to distinguish which version of the
21 product is intended for market, and deciphering
22 tobacco product naming conventions can also be

1 problematic.

2 Another significant challenge that
3 impedes progress is the applicants have sent new
4 study data and large amendments to FDA for review
5 towards the end of FDA's scientific review phase.
6 Reviewing additional information has caused
7 delays in FDA issuing marketing/no marketing
8 orders.

9 I've discussed a lot of information in
10 a short amount of time. I hope that you've found
11 the information helpful in your effort to develop
12 a quality PMTA submission. Up next is my
13 colleague Dr. Callahan-Lyon. She will provide in
14 her presentation examples of informative studies
15 and other supportive information from the IQOS
16 submission. Thank you for your time.

17 (Applause.)

18 DR. CALLAHAN-LYON: Hi, good
19 afternoon. I'm Priscilla Callahan. I'm the
20 deputy director for the Division of Individual
21 Health in FDA's -- oh sorry. I'll start over.

22 I'm Priscilla Callahan. I'm deputy

1 division director in Division of Individual
2 Health Sciences, CTP's Office of Science. I'm
3 going to discuss some information regards to the
4 IQOS submission and specifically what kinds of
5 information they used in that submission that
6 allowed us to authorize marketing of the product
7 as a PMTA.

8 So just for those that may not know,
9 IQOS is a non-combustion cigarette product. It
10 includes a HeatStick, a holder and a charger.
11 The tobacco is heated with this product. It's
12 not burned or combusted, and I've included a
13 picture of the device and the holder and the
14 HeatStick packaging here.

15 So what types of information did they
16 include in their applications? I'm going to go
17 through this at a very high level, keeping in
18 mind the kinds of things that Ms. Holmes just
19 discussed in her PMTA presentation. I also have
20 included on some of the slides just you'll see a
21 note in a red circle, just hints and other
22 suggestions that you might consider in your PMTA

1 applications for the future.

2 So with regards to engineering data,
3 they provided us a complete description of the
4 product designs and parameters, as well as
5 manufacturing steps and quality control measures.
6 They also outlined very clearly the process,
7 controls and quality assurance measures to ensure
8 that the products met manufacturing
9 specifications that were set by the applicant,
10 and that they would be manufactured in a
11 consistent manner.

12 There was performance standards and
13 performance testing to verify product design, and
14 specifications and independent test results for
15 the battery were conducted by FDA and found to be
16 satisfactory.

17 With regards to chemistry, they
18 provided a complete list of the uniquely
19 identified components, ingredients and additives
20 with applicable specifications and a description
21 of the intended function of each of these
22 materials, as well as a description of the steps

1 and the quality control measures, and evidence of
2 product stability including microbiological
3 testing.

4 The testing data for certain HPHCs was
5 included in the applications. These are some of
6 the ones that were included. But I have from a
7 note here "Applicants should provide data that
8 will assist FDA in determining their product is
9 APPH and the specific types of information needed
10 may vary, depending upon the product type.

11 With regards to the toxicological risk
12 assessment, the applications included measures of
13 HPHCs in the aerosols and compared it to 3R4F
14 cigarette smoke. They also made comparisons for
15 HPHCs and tar to U.S.-marketed cigarettes. They
16 included measures of nicotine in the HeatSticks
17 and the aerosol, as well as non-targeted
18 differential screening assays, and in vitro and
19 in vivo studies.

20 For the behavior and clinical
21 pharmacological assessment, four PK/PD studies
22 were included in the applications. There were

1 also four exposure studies, two of which lasted
2 for five days and two of which lasted for 90
3 days, and one actual use study. Another note:
4 information to consider may include nicotine
5 exposure relative to other tobacco products,
6 abuse liability, the attractiveness and
7 likeability of your product, and the likelihood
8 of switching and/or use of multiple products.

9 For individual health impact, they
10 included quite a lot of information. We had the
11 four exposure studies that were mentioned
12 earlier, and these did include measures of
13 biomarkers of exposure. The biomarkers of
14 exposure were selected by the applicant to
15 correspond with 14 HPHCs and nicotine and
16 nicotine alkaloids.

17 They were assessed after a five day
18 confinement period and also after a 90-day
19 ambulatory period and compared results were given
20 for studies conducted in the United States and in
21 other countries where the product is currently
22 marketed.

1 As regards to biomarkers of potential
2 harm, they selected these and these were also
3 selected by the applicant on the basis of key
4 mechanisms for three smoking-associated diseases,
5 cardiovascular disease, COPD and lung cancer.
6 The applicant selected these and provided the
7 rationale as well as significant literature on
8 the selected BOPHS and the relationship with the
9 diseases of interest.

10 Other individual health impact
11 measures included adverse experiences associated
12 with the acute exposure in the clinical studies,
13 an actual use study to evaluate uptake and use in
14 the current U.S. adult cigarette smokers,
15 consumer reports and complaints from countries
16 where their product is currently marketed, an
17 updated literature review during the course of
18 the application review with case studies and
19 other reports, and they also provided long term
20 six month continuation of one clinical study,
21 with long-term BOE and BOPH data, and information
22 on uptake, continued use and dual use.

1 Not all of these may be needed for any
2 particular product application, so what you need
3 to consider is what information FDA needs in
4 order to determine that marketing of the product
5 is APPH and how it can best be provided.

6 With regards to other factors under
7 individual health, we consider the human factors.
8 This was discussed to some degree by Ms. Holmes.
9 This is the way people will actually use the
10 product, an actual use study to assess product
11 misuse, as well as an evaluation of the advanced
12 device malfunctions and other potential for
13 serious issues.

14 The applicant also included consumer
15 comprehension study of the labeling and what they
16 did with this was by a study evaluating the
17 ability of prospective customers to understand
18 and comply with product instructions. This is
19 another note.

20 The type of human factor studies and
21 comprehension testing may vary, depending on the
22 product type and the potential for misuse, and

1 may also be important to demonstrate that the
2 product is unlikely to expose high risk groups
3 such as children.

4 With regards to population health, we
5 have to consider several things and you've heard
6 these today. Number one is the likelihood of
7 product use by current cigarette smokers, so in
8 this particular application they included a
9 perception study with different brochures with
10 package labeling and warning statements, and the
11 study included smokers, former smokers, never
12 smokers and young adult never smokers.

13 Information was also submitted with
14 the actual use study, which evaluated use of the
15 product in the United States, and included
16 product initiation and use patterns as well as
17 dual use and switching over a period of six
18 weeks. Whole offer testing was their term for a
19 product study that was conducted outside of the
20 United States, and evaluated product initiation
21 and use patterns in other countries where the
22 product was already currently marketed.

1 With regards to polyuse of the product
2 with cigarettes or other tobacco products, the
3 applicant provided data from two different post-
4 marketing surveys in a country where the product
5 is already marketed, as well as additional data
6 from the actual use study and the clinical
7 studies.

8 With regards to the likelihood of the
9 use of the product leading to cigarette smoking
10 cessation, again we had information from the
11 actual use study and the whole offer test, as
12 well as post-market survey information. Other
13 population health impact studies that were
14 included were uptake of the product by former and
15 never smokers or youth. This is obviously of
16 great interest to FDA.

17 So the perception study did provide
18 some information with regards to the intent to
19 try the product in former smokers, never smokers
20 and young adult smokers or never smokers. The
21 cross-sectional studies were also conducted to
22 monitor prevalence of this in similar products in

1 adult non-smokers. There was some data from
2 outside of the United States where the product is
3 currently marketed, as well as face to face
4 survey data that were presented from a different
5 country, where participants as young as 15 years
6 old were surveyed on their likelihood of use of
7 the product.

8 Of note, there was no specific U.S.
9 data provided for youth. In this particular
10 situation, FDA must consider the likelihood that
11 those not using the tobacco product will start
12 using the product, and although youth studies are
13 not specifically required, we do need you to
14 consider how the information that you can provide
15 will be used to support this particular aspect of
16 FDA review.

17 Marketing plans were included in the
18 applications. These were very high level and
19 provided a general approach to their marketing
20 strategy with sample labeling. They also
21 clarified at our request their strategy for
22 limiting youth exposure and hopefully uptake of

1 the products.

2 In addition, in the post-marketing
3 reporting period, which was included in the
4 marketing authorization letter, we provided
5 requirements for them to provide FDA with
6 periodic reports of product sales and
7 distribution by location, market type and product
8 type. We also included the situation where they
9 will provide prior notification to FDA for
10 marketing plans and materials.

11 They will provide an analysis of
12 delivery of advertising impressions by age
13 breakouts. Adverse health reports will be
14 included in period reporting, as well as other
15 consumer complaints, especially those regarding
16 product quality.

17 So in summary, I'm going to go back to
18 some of the points that have been made before, it
19 is very, very important that you include all of
20 the information in your original submission. As
21 has been mentioned several times, amendments are
22 challenging. Each amendment must be evaluated as

1 to whether it's major or minor, and major
2 amendments can prolong your product review and
3 delay a decision.

4 The other point I want to make is that
5 it's important to provide FDA a very clear
6 picture that we can follow during the application
7 review, using consistent terminology such as
8 product naming, study name, consistently
9 throughout the application makes it very helpful
10 and is much easier for us.

11 Organizing the data and provide an
12 accurate table of contents with all the codes and
13 definitions and other materials that we need in
14 order to review the applications. If you're
15 bridging data, provide a rationale and clear
16 explanation for why this is important for your
17 particular product, and clearly describe your
18 approach, the study methods, the approach to the
19 statistical analysis, the literature search
20 methods and terms and anything else that you
21 think would make it easier for us to review your
22 applications. Thank you.

1 (Applause.)

2 MS. RADWAY: Thank you again to Ms.
3 Holmes and Dr. Callahan-Lyon. Next, we will have
4 Ms. Christine Saba discussing PMTA Post-Marketing
5 Requirements.

6 MS. SABA: Okay. I believe I'm the
7 last presentation of the day, and so I will try
8 and keep my remarks brief, to get everybody out
9 of here on time. Today, I will be presenting the
10 proposed premarket tobacco product application
11 post-market reporting requirements for industry.

12 On September 25th, 2019, FDA gave
13 notice of a proposed premarket tobacco
14 applications and recordkeeping requirements rule,
15 the PMTA NPRM. This proposed rule is available
16 and open for public comment through November
17 25th, 2019. This presentation will review post-
18 market reporting requirements outlined within the
19 PMTA NPRM. Note these are subject to change
20 within the final rule.

21 PMTA NPRM Subpart D outlines the
22 proposed post-market reporting requirements.

1 Applicants would be required under this proposed
2 section to submit two types of report to FDA
3 after receiving a marketing order, periodic
4 report and adverse experience reports.

5 Applicants would need to submit
6 periodic reports within 60 calendar days of the
7 reporting date specified within the marketing
8 order. Adverse experience reports would be
9 required to be reported to FDA within 15 calendar
10 days of receipt or identification. It is
11 proposed that the report include the following:
12 A cover letter that contains the PMTA STN,
13 tobacco product name or names, the company name,
14 date of report and the reporting period.

15 The proposed rule states that each
16 post-market report must be well-organized,
17 legible and written in English. Documents that
18 have been translated from another language into
19 English such as original study documents written
20 in a language other than English must be
21 accompanied by the original language of the study
22 documents, as well as a signed certificate from

1 the manufacturer certifying that the English
2 language translation is complete and accurate.

3 As mentioned, the PMTA NPRM proposes
4 two types of reports that an applicant would be
5 required to submit following a marketing order,
6 periodic reports and adverse experience reports.
7 FDA anticipates that periodic reports would be
8 required on an annual basis, but FDA may require
9 in a specific order that reports may be made more
10 or less frequently, depending on a number of
11 factors such as the novelty of the type of
12 product.

13 This slide presents a high level
14 overview of the proposed data elements for each
15 report. Adverse experience reports would include
16 reporting of serious adverse experiences such as
17 death, life-threatening event, inpatient
18 hospitalization, incapacitation of user, birth
19 defect, any other adverse or serious condition
20 affecting quality of life, as well as unexpected
21 adverse experiences.

22 Each of these would be required to be

1 reported to FDA within 15 calendar days of
2 receipt or identification. Periodic reports
3 include the following broad proposed data
4 categories: a description of the changes made to
5 the manufacturing facilities or controls that do
6 not modify the finished tobacco product,
7 inventory of ongoing and completed studies of the
8 tobacco product, a summary of sales and
9 distribution data, data on current product
10 purchasers, final labeling specimens and labeling
11 changes, marketing and advertising implementation
12 plans and reports. These reports will be
13 discussed in more detail in the upcoming slides.

14 First, we will cover adverse
15 experience reporting. The PMTA NPRM proposes the
16 applicant report all serious and unexpected
17 adverse experiences associated with the tobacco
18 product that have been reported to the applicant
19 or that the applicant is aware of to CTP's Office
20 of Science through the HHS Safety Reporting
21 Portal within 15 calendar days after the report
22 is received by the applicant.

1 Qualifying serious adverse experiences
2 were listed in the previous slide, so I won't
3 repeat them again. Unexpected adverse experiences
4 would also be required to be reported. FDA's
5 proposed definition for unexpected adverse
6 experience can be found in Subpart A of the PMTA
7 NPRM. This reporting also includes manufacturing
8 deviations.

9 For products that have been
10 distributed, if a deviation occurs that presents
11 a reasonable probability that the tobacco product
12 contains a manufacturing or other defect not
13 ordinarily contained in tobacco products on the
14 market that could cause serious adverse health
15 consequences or death, the applicant would be
16 required to report this deviation to FDA within
17 15 calendar days of identification.

18 Now we'll cover periodic reporting in
19 more detail. The PMTA NPRM proposed periodic
20 reporting requirements for manufacturing changes,
21 deviations and adverse experiences include a
22 summary and analysis of serious and unexpected

1 adverse experiences identified during the
2 reporting period, accompanied by a statement of
3 any changes to the overall risk associated with
4 the tobacco product and a summary of any changes
5 in the health risks, including the nature and
6 frequency of the adverse experience, as well as
7 potential risk factors.

8 It should include a summary of all
9 manufacturing deviations, including those
10 associated with the processing, testing,
11 packaging, labeling, storage, holding and
12 distribution. Note that serious adverse
13 experiences and manufacturing deviations that may
14 cause serious adverse health consequences should
15 be reported to FDA twice through the safety
16 reporting portal as events are initially received
17 and again for periodic reporting.

18 A summary of changes made to the
19 manufacturing facilities or controls that do not
20 modify the finished tobacco product such as
21 manufacturing process changes compared to what
22 was submitted into the PMTA should also be

1 reported, as well as a rationale for each change.
2 FDA issues marketing orders for the specific new
3 tobacco product described within the PMTA. An
4 applicant may not make any modification including
5 a change in design, any component, any part or
6 any constituent including a smoke constituent or
7 in the content delivery or form of nicotine, or
8 any other additive or ingredient to the product
9 that is the subject of the order.

10 Any modification to the tobacco
11 product that would result in a new tobacco
12 product under the definition in Section 910(a)(1)
13 of the FD&C Act would require the applicant to
14 submit a new tobacco product application for the
15 modified tobacco product.

16 Changes that do not result in a new
17 tobacco product, such as manufacturing product
18 changes that do not modify the finished product
19 would be required to be reported under periodic
20 reporting as described in Subpart D of the PMTA
21 NPRM.

22 FDA may notify an applicant that FDA

1 has determined that a change described in a
2 periodic report results in a new tobacco product
3 outside the scope of the marketing order,
4 requiring the submission of a new tobacco product
5 application and issuance of a new marketing order
6 if the applicant seeks to market the new tobacco
7 product, unless that tobacco product can be
8 legally marketed through a different premarket
9 pathway.

10 Applicants seeking to make
11 modifications to the tobacco product authorized
12 under a standing order may submit a standard
13 PMTA, a supplemental PMTA or request for an
14 exemption from substantial equivalence for the
15 modified product in order to seek marketing
16 authorization for that new product.

17 Supplemental PMTAs are based on a
18 cross-referencing system to reduce the burden of
19 both preparing and reviewing a PMTA. Note that
20 the applicant may not market the new tobacco
21 product unless FDA has authorized its marketing.
22 Failure to do so would render it adulterated

1 under Section 910(f) of the FD&C Act, and would
2 be subject to enforcement action.

3 The PMTA NPRM proposes the applicant
4 report the following: an inventory of all
5 ongoing and completed studies about the tobacco
6 product conducted by or on behalf of the
7 applicant that were not already submitted as part
8 of the PMTA or previous post-market reports.

9 Full reports of information published
10 or known to or which should be reasonably known
11 to the applicant concerning scientific
12 investigations and/or literature about the
13 tobacco product that were not previously
14 submitted as part of the PMTA or previous post-
15 market reports, as well as significant findings
16 from publications that have not been previously
17 reported to FDA.

18 An assessment of how the product
19 continues to be appropriate for the protection of
20 public health would be required. When
21 determining whether the marketing of a particular
22 new tobacco product would be appropriate for the

1 protection of public health, FDA will evaluate
2 the factors in light of available information
3 regarding the existing tobacco product market,
4 tobacco use behaviors and associated health risks
5 at the time of review.

6 The PMTA NPRM proposes the reporting
7 of a summary of sales and distribution data of
8 the tobacco product to the extent that the
9 applicant collects or receives such data for the
10 reporting period including total U.S. sales
11 reported in dollars; units and volume, with
12 breakdowns by U.S. Census region, major retail
13 markets and channels in which the product is
14 sold; the universal product code or codes that
15 correspond to the products or product identified
16 in the PMTA; and demographic characteristics of
17 product purchasers such as age, gender and
18 tobacco use status.

19 Proposed requirements for labeling and
20 advertising include specimens of all labeling and
21 descriptions of all labeling changes that have
22 not been previously submitted to FDA, including

1 the date the labeling was first disseminated and
2 the date when dissemination was completely
3 terminated, as well as full color copies of all
4 advertising for the tobacco products that have
5 not been previously submitted to FDA, as well as
6 the date the materials were first disseminated
7 and the date the dissemination was completely
8 terminated.

9 The proposed reporting requirements
10 for reporting marketing and advertising plans
11 include a description of the implementation of
12 all advertising and marketing plans by channel
13 and by product, including a dollar amount of each
14 such plan, including a description of any use of
15 competent and reliable data sources,
16 methodologies and technologies to establish,
17 maintain and monitor highly targeted advertising
18 and marketing plans and media buys; use of owned,
19 earned, shared media, public relations outreach,
20 paid social media, partners, influencers,
21 bloggers or brand ambassadors to create labeling
22 for, advertise, market or promote the products;

1 consumer engagements conducted by the applicant
2 or on its behalf or at its direction, including
3 events at which the products were demonstrated;
4 as well as an analysis of actual delivery of
5 advertising impressions including breakouts by
6 age ranges to the extent that this is applicable.

7 Additional proposed reporting includes
8 a description of any targeting of specific adult
9 audiences by age range including young adults
10 ages 18 to 24, and other demographic or
11 psychographic characteristics that reflect the
12 intended target audience, including a list of all
13 data sources used to target advertising and
14 marketing plans and media buys, as well as
15 actions taken to restrict youth access and limit
16 youth exposure to the product's labeling,
17 advertising, marketing or promotion.

18 PMTA NPRM proposed Section 1114.31(b)
19 would allow FDA, using its authority under
20 Section 910(f) of the FD&C Act, to require an
21 applicant to submit post-market reports in
22 addition to those described in PMTA NPRM Subpart

1 D, including but not limited to requirements that
2 an applicant provide information such as
3 labeling, advertising, marketing or promotional
4 materials or marketing plans not previously
5 submitted to FDA, and to do so at least 30 days
6 prior to the initial publication, dissemination
7 to consumers or use in engaging or communicating
8 with consumers of such materials.

9 In conclusion, the data described in
10 PMTA NPRM Subpart D are especially important for
11 FDA to review, because the data inform the
12 determination of whether or not the new product
13 continues to be appropriate for the protection of
14 public health. In particular, the data help FDA
15 to assess whether the information regarding
16 likely tobacco product use behavior described
17 within the PMTA lines up with actual use of the
18 product after authorization.

19 For example, if youth initiation rates
20 associated with the new tobacco product are not
21 what was anticipated within the PMTA, FDA may
22 decide that the product is no longer appropriate

1 for the protection of public health and the
2 marketing authorization may be withdrawn.

3 Finally, please note that PMTA NPRM is
4 open for public comment until November 25th,
5 2019, although similar to other NPRMs the comment
6 period for this may be extended. Applicants may
7 review the IQOS marketing authorization as a
8 reference for post-market reporting requirements,
9 but exact requirements of a marketing order can
10 vary. Thank you.

11 (Applause.)

12 MS. RADWAY: Thank you Ms. Saba. So
13 this concludes our content for today. A special
14 thank you to all the presenters and panelists,
15 and all those submitting questions. As a
16 reminder, tomorrow the room that we have will be
17 much smaller, so keep that in mind, and we'll
18 pick back up tomorrow on the next part of Session
19 3, starting with a presentation. Thank you.

20 (Applause.)

21 (Whereupon, the above-entitled matter
22 went off the record at 3:08 p.m.)

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In the matter of: Deemed Tobacco Product
Applications: Public Meeting

Before: US FDA

Date: 10-28-19

Place: Silver Spring, MD

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