U.S. FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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PREMARKET APPLICATIONS: OPPORTUNITIES FOR STAKEHOLDER ENGAGEMENT

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PUBLIC MEETING

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MONDAY
OCTOBER 23, 2023

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

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

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

9:01 a.m.

DR. KING: Good morning, everyone, if you could please take your seats. We're going to get started as promptly as possible. There's plenty of room here in the room. Feel free to come up to the front, we don't bite. We may call you up for audience participation, but that's the worst of it.

Okay, so good morning, everyone. I am Brian King, I am the Director of the Center for Tobacco Products. It's a thrill to see you all today. Many folks in person here in the room and many more virtually for this hybrid meeting. I believe we had over 800 people register, which is quite remarkable. So we're looking forward to the meeting over the next couple days.

In terms of background, many folks know that we had an external evaluation from the Reagan-Udall Foundation last year. And as part of that process, there was a report with 15 recommendations.

And of those there were several related to our Office of Science, some particularly around

application review. And there was also an overarching comment around transparency, which was heard loud and clear.

That said, we're committing to address all 15 of those recommendations, and we've developed a website to highlight the key areas where we are focusing on those efforts. And we continue to update that on a quarterly basis.

So, I will say that the last one was midsummer, so if you do the math, you can expect another update on our progress very soon, and we're committed to continuing those in the -- for the imminent future.

That said, I do want to comment briefly on the transparency issue. And I do think it's a two-way street. And the first way is definitely on the part of the Center for Tobacco Products.

And we're very committed to ensuring that we are not only communicating effectively, but also engaging with stakeholders. And I think today is a prime example of that.

I will say that this is not the first

time that we've had a public meeting or a workshop, and it certainly won't be the last. That said, I think that we're all getting back into the swing of things as we extricate ourselves from post-pandemic realities.

And I'm hopeful that we can start to include these as part of our routine portfolio related to content related to the Office of Science. But also, other offices as well.

That said, we have a very good lineup for you.We have several colleagues from Office of Science. They have put them behind this gate here. They don't bite though, they will be coming out. I would encourage you to engage throughout the day.

And we've got a lot lined up in terms of identifying one, best practices related to application submission in the review process, particularly related to our experiences over the past several years as we have honed the process. That said, we also have opportunities for lessons learned.

We've now gone through nearly all of the 26 million e-cigarette applications that have come

in. And as part of that there are lessons learned in efficiencies. And towards that end, we also have some new resources that we'll be talking about.

One recently is the validator tool that I know some folks have already started to use, which I think is very important for efficiencies on both ends in terms of making sure that we give you the resources you need to avoid errors in terms of submissions of applications. But also on our end to make things more expedient so that we're not having to go back to address those matters.

And so there's a variety of different aspects that I'm very hopeful you will find helpful through today's session.

But as I noted, it's a two-way street, and I will say the other street is you all. And I really will strongly encourage you to engage today. It is a two-day session. I'm not a big fan of death by PowerPoint, and so it's a bad way to go. I encourage you to really engage.

We're going to have a lot of opportunities after every session in terms of

answering some of the questions that we received when you submitted your registration. But we're also going to have live Q&A as well, where you can engage from our staff from the Office of Science.

And really encourage you to take that opportunity. It's critical that we do have this transparency across both ways. If we don't know that there are issues, we can't help to address them. And there's also key matters that we want to make sure you're aware of to make your lives easier in terms of the submission process.

So that said, we've got a lot going on. I'm very excited over the next few days. I unfortunately will not be here for the duration. I've got to jet out, I've got a few meetings and then I get to head to Omaha, Nebraska, within in a matter of hours.

But I will be attending remotely and also will receive updates. So appreciate all the time that you all are dedicating over the next few days. And thanks again for attending.

And before turning it over, I did want to

also thank the folks that created all the work and developed and implemented these meetings. It is a hell of a lot of work, folks. And it's very easy to say convene a meeting, but in the federal, glacial processes, that's a lot.

And so I commend all of our folks from Office of Science who have diligently planned today. It's a great session with a lot of content for a diverse array of staff from across the Center. And I look forward to the time today.

So thanks again to them, thanks again to you all. And I look forward to a productive, collegial, and efficient use of the next couple days.

And with that, I'm going to turn it over to my colleague, Avena Russell, who is going to be our moderator for the next two days. Thanks all, folks, bye.

CDRCDR RUSSELL: Good morning, and thank you, Dr. King. We want to echo, I want to echo his warm welcome and opening remarks. Thank you all to our stakeholders. This includes those who are virtually and who are here with us face to face.

Thank you for taking the time to spend your day with us.

My name is Commander Avena Russell, and I will serve as your moderator for today. I am a Commissioned Officer in the United States Public Health Service. I serve as a Branch Chief in the Office of Science, Division of Regulatory Project Management. I will be your moderator for two days. So you guys have me for two days.

Before we begin, I would like to go over a few logistics of the day and to provide you with the layout for our structure of the meeting. I also will provide you with our purpose and our goals for this meeting.

For today, we will break only once before lunch. We anticipate breaking for lunch on or about noon. Lunch options will be available for purchase outside in the cafeteria or in the lobby. But please keep in mind these options are limited.

This meeting is being recorded and a transcript will be provided and posted on CTP's website after the meeting.

For the logistics, to our stakeholders, CTP would like to hear from you. As part of the registration process for this meeting, we provided an opportunity for you to submit questions in advance. We received several suggestions from our stakeholders on guidances and regulations that would be of interest to you.

If you have suggestions on premarket review topics, please provide them to us. Future -- we would also like to have future regulations or guidance or any topics that are not covered specifically within the scope of this meeting. You may send your suggestions to CTPregulations@fda.hhs.gov. This email address is posted outside on the registration table.

The purpose of this meeting is it is intended to provide the agency's expectations for tobacco product premarket applications, with a particular focus on stakeholder engagement and providing clarity on application submissions criteria.

It should be noted that FDA does not

intend to address or discuss anything outside of the scope of this meeting. This includes any pending applications or litigation, future rulemaking, potential enforcement discretion policies, or any new policy not previously communicated and guidance documents for rulemaking.

Following each group presentation, we will hold a panel discussion that includes subject matter experts from the Office of Science. Questions will not be taken during any of the presentations, but rather addressed during the panel discussion.

We will take live questions from our onsite audience and virtual participants for the panels that follow the presentation. Your questions should be relevant to the content discussed within the presentation prior to the panel. We will ask that you introduce yourself and state your organization prior to asking questions.

For those in the virtual audience, you may submit your questions via the chat function.

For day two only, during the last panel session, FDA will be answering questions that were

received as part of the registration process. In addition, we will be accepting questions throughout the day and throughout the duration of this meeting until lunchtime tomorrow.

Those questions submitted will also be answered during the panel session on day two. For your convenience we have index cards available at the registration table and various FDA staff will be available throughout this room to provide you with resources to write those questions down. You may feel free to hand your index cards to any of the FDA staff who will be collecting the cards throughout the audience.

When writing your questions, we ask that you speak clearly, communicate what you ask, and write as neat as possible. Also, please identify yourself and the organization on your index card. If your questions do not get answered during the panel discussion or you have additional questions, you can submit those questions to askctp@fda.hhs.gov.

We will now begin the presentation portion of this meeting. Session 1. Session 1 will

discuss premarket tobacco applications, where we are, and what we're looking forward to.

The first presentation will be an overview of the PMTA process by Huda Dawood, followed by Eric Cruz providing an overview of the status of PMTAs.

Let's welcome Ms. Huda Dawood.

MS. DAWOOD: Thank you, Avena. Hello, everyone, and good morning. My name is Huda Dawood, I am a Regulatory Health Program Manager from the Division of Regulatory Project Management in the Office of Science.

Today I will be presenting on an overview of premarket tobacco product applications, also known as PMTAs. First, I will go into some background and describe the statutory requirements.

I will then briefly explain the review phases for this program. Finally, I will end with a discussion of some key features and wrap up with various resources that CTP has made available to applicants.

To begin, I will discuss the statutory

requirements for a PMTA as described in Section 910 of the Federal Food, Drug, and Cosmetic Act and the types of PMTAs that an applicant may submit.

An order under Section 910(a)2 is required to legally introduce and legally market a tobacco product in the United States. The PMTA pathway is the primary pathway for a new tobacco product to come to market.

This is based on Section 910, which requires authorization for new tobacco products through a 910(b) application, unless the product has a substantial equivalence, or SE order, or has been found exempt from demonstrating substantial equivalence, or EX, by FDA.

The PMTA pathway is used for new products that do not have a valid predicate product for comparison. Please note that a new tobacco product that receives a marketing order via the PMT pathway cannot be used as a predicate product for an SE application.

Currently, FDA prioritizes enforcement of the requirements of Section 910 to finished

tobacco products, including components and parts of deemed products sold or distributed separately for consumer use.

FDA generally does not at this time intend to enforce these requirements for components and parts of deemed products that are sold or distributed solely for further manufacturing into finished tobacco products and not sold separately to the consumer.

There are three different types of PMTAs: standard, supplemental, and resubmission. A standard PMTA is the primary type of submission for new products. An applicant would have to first submit a standard PMTA for which OS must complete review of before an applicant may utilize the other two types.

A supplemental PMTA can be submitted in situations where an applicant is seeking authorization for a new tobacco product that is a modified version of a previous -- of a product that previously received a Marketing Granted Order.

A resubmission can be submitted to address application deficiencies following the

issuance of a Marketing Denial Order. A resubmission cannot always be used to address application deficiencies, and it is important to review the marketing denial letter to see if this is an option for use.

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

First is if marketing of the product is appropriate for the protection of public health. Consideration for this is determined with respect to the risks and benefits to the population as a whole, including users and non-users of the tobacco product.

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

The other three considerations of our review are the conformance to the requirements that

apply to Section 906(e), which deals with manufacturing practices. The proposed labeling should not be false or misleading, which may render the product misbranded under Section 903.

And finally, the product must conform to any product standards under Section 907 which apply, or the application must contain an adequate justification for such deviations.

Now that we have covered some basics, I will walk through the review phases of the PMTA. The PMTA review process is divided into five distinct phases. Just a note that the flags here represent the phases, however, they are not necessarily to scale and do not indicate the portion of time required for review.

Phase 1, which is not required but strongly recommended, is the pre-PMTA meeting. Phase 1 is the acceptance review. Phase 2 is the filing review. Phase 3 is the review and action phase. And finally, Phase 4 is the post-market reporting phase.

As described in Section 910 CU1(a) of the Federal Food, Drug, and Cosmetics Act, the PMT pathway

has a 180-day review period. Now I will describe the phases of the review process.

Phase 0 of the submission review process is the pre-PMTA meeting between the applicant and FDA. It is considered Phase 0, as this is not required for PMTA submission.

However, CTP encourages applicants to request appropriate meetings, as we find that after meeting with FDA, an application may be more likely to be complete at the time of submission and likely to be accepted and filed.

FDA recommends that a meeting be held well in advance of the planned premarket submission so that the applicant has the opportunity to consider CTP discussion points and feedback prior to preparing their full application.

This may include but is not limited to a discussion on appropriate samples, inspections, discussion on end points, and any clarifying questions.

CTP issued a revised guidance in September of 2022 on meetings with industry and

investigators on the research and development of tobacco products, which may provide further information on how to plan, request, and what to expect from meeting with the Office of Science.

Phase 1 in the review process is the acceptance phase. During the acceptance, CTP will review the application to make -- to ensure the product falls under our jurisdiction. Regulatory Health Project Managers, or RHPMs, complete this preliminary review to determine if the application meets all statutory and regulatory requirements applicable to PMTAs.

At the end of Phase 1, there are two outcomes. We will either accept or refuse to accept, or RTA, a submission. If the application is missing a required element, the applicant will receive a refuse-to-accept letter, which will include the reasons for the refusal. An RTA results in closure of the application.

If the applicant wants to market the product, they must submit a new application for the products. If refused, the applicant may submit a new

application once they are able to provide all of the statutory and regulatory requirements of the application.

If the application appears to contain all of the required elements, CTP will issue an acceptance letter, which will inform the applicant that their application has been accepted by the agency, the RHPM assigned to the application, and that their application will move forward in the review process.

Just a note on the role of the RHPM. We are your main point of contact for any issues related to your applications and are the person that should be contacted should you have any questions. The acceptance letter will provide contact information.

If the application is accepted by CTP, it moves to the next phase, which is filing review. Phase 2 is the filing stage. The purpose of the filing review is to determine if the application contains the necessary information to initiate substantive review. FDA will conduct a more in-depth multidisciplinary review of the data as submitted to determine if all statutory and regulatory

requirements have been met.

A PMTA may not be filed if the PMTA does not contain sufficient information required by Section 910(b)1 of the Federal Food, Drug, and Cosmetic Act, and by Sections 1114.7, 1114.15, or 1114.17, as applicable, to permit a substantive review of the application, and/or the application does not contain any substantive information, including information from published literature or abridged from an investigation of another tobacco product regarding each of the following topics: health risks of the new tobacco product, health risks of the new tobacco product compared to products in the same category and at a least one product in a different category, abuse liability of the new tobacco product, how consumers would actually use the product, impact of marketing on likelihood of current users changing behavior, impact of labeling and advertising on current non-users of tobacco product, impact of labeling and advertising on individuals' perception and use intentions, and finally, how human factors can affect health risks of the new tobacco

product.

Here you see the filing requirements broken out by what is required from the statute or the Tobacco Control Act, and examples of what has been added with the PMTA final rule. A later presentation by Eric Cruz will cover changes from the PMTA rule. I will focus on the statutory requirements.

The first section displays the statutory requirements. These requirements apply to all PMTAs received prior to November 4, 2021, including those applications submitted for the deeming bolus.

Although a full description of all information pertaining to investigations of the health risks of the product and tobacco product samples are required for filing, to streamline our review, we included this in our Phase 3 or a substantive scientific review.

Additionally, we moved samples assessment to Phase 3. The rationale to support review of samples in full scientific review was to ensure that the correct number of samples was requested prior to

industry submitting samples for storage. This ensured that samples are only sent once and processed quickly upon receipt.

During our review of applications received pre-rule, we focused on the presence or absence of: full statements of components, ingredients, additives, and properties and of the principle or principles of operation.

Full description of the methods used in, and the facilities and controls used for the manufacture, processing, and when relevant, packing and installation; specimens of the labeling proposed to be used; and an adequate environmental assessment, or EA, for a tobacco product application.

Eric Cruz will cover how filing has changed since the implementation of the PMTA rule.

At the end of this phase, similar to the acceptance phase, CTP will issue one of two types of correspondence. If the submitted information is inadequate to continue with substantive review, the applicant will receive a refuse-to-file letter, which will include the reason for the refusal.

If refused, the applicant has the option to submit a new application once they are able to meet the filing requirements for a PMTA seeking a marketing order.

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

Now that the application has been filed, we initiate Phase 3, the substantive review phase. This review phase is a multidisciplinary approach to review the data submitted by the applicant and determine if such data is sufficient to demonstrate that authorizing the marketing of the product would be appropriate for the protection of the public health as previously described.

During the review phase, CTP may conduct inspection, such as of clinical or manufacturing facilities, in conjunction with CTP's Office of Compliance and Enforcement, or OCE. Additionally,

testing of the new product may be conducted by FDA.

An application may be referred to the Tobacco Products Scientific Advisory Committee, or TPSAC. If the applicant would like CTP to consider referral, they should include the request in the cover letter of the initial submission.

It would also be helpful to provide rationale for why FDA should refer the application to TPSAC. However, CTP makes the decision on whether to refer a product under consideration to TPSAC and will determine this during the review phase.

Flavored ends pose a significant risk to non-users, especially youth. FDA has determined that this risk is substantial, and this is well-established by existing scientific literature.

FDA determined that the risk for flavored ends could only be overcome by robust and reliable evidence demonstrating that the new flavored products provided an added benefit relative to tobacco-flavored ends, for adult smokers in terms of complete switching or significant cigarette reduction.

In order to assess whether an application

demonstrates this added benefit to adult smokers, CTP has developed a flavored ends review, or FE review.

It is important to note that this review is only for certain products. It does not include ends with a tobacco-only flavor, nor ends components that do not contain an e-liquid. Additionally, it was not used for categories of products outside of ends.

OS commenced this targeted review, which determines presence or absence of the types of evidence deemed necessary to demonstrate an added benefit to adult smokers of flavored ends products.

Applications that include this information may be referred for further substantive scientific review if they meet other filing criteria. More information on this review will be provided tomorrow.

After the completion of scientific review, FDA will determine if marketing of the product under review is appropriate for the protection of public health.

In general, within 180 active FDA review

days, an applicant will receive notification from FDA either granting or denying marketing authorization unless issues are identified in the application that require response from the applicant. More information on this and other updates will be discussed on the next slide.

If marketing authorization is denied, the reason leading to that decision will be provided. The applicant may have the opportunity to resubmit their application, or the applicant could submit a new application.

If authorized, the applicant will be provided a marketing order notifying the applicant that the new tobacco product is appropriate for the protection of public health and you have met the other requirements of Section 910(c) of the FD&C Act.

Under the provisions of Section 910, you may introduce or deliver for introduction into interstate commerce the new tobacco product. Any restrictions on sales and distribution will be described in the marketing order.

One additional point. There may be

instances where the application supports issuance of a Marketing Granted Order but we need additional information to satisfy the National Environmental Policy Act, or NEPA.

In this situation, FDA will issue an environmental information request letter. Once the NEPA items have been resolved, FDA can then move forward with a marketing authorization.

In addition to adding cycles and creating the flavored ends review, OS implemented changes to make PMTA review more efficient. Please note that FDA generally intends to deny any extension request for more time to respond to deficiencies.

The expectation is that if significant information is needed for an application, the applicant can always resubmit at a later date.

Due to the large number of applications and resource limitations, OS developed a process for prioritizing applications for review. In general, OS prioritizes application reviews in the following way.

PMTAs are placed in three queues. Queue 1 is for PMTAs, for ends products from manufacturers

with the largest market share. Within this queue, OS will prioritize earliest PMTAs received from each manufacturer. Over time as other products gain market share, they may be added to this queue.

Queue 2 is for PMTAs for all marketed, deemed, and statutorily regulated tobacco products not in Queue 1. Within this queue, OS will select PMTAs for review by randomizing each manufacturer.

And finally, Queue 3 is for PMTAs for deemed and statutorily regulated tobacco products not currently marketed and incorporate age-verification technologies to prevent youth access. In the past, OS has called these products of merit. One example would include an ends product that promotes age-gating via a new technology.

Issues may arise where a PMTA is selected for review for reasons not outlined in Queues 1-3. For example, due to work from other offices or to support another office's work, FDA is currently reevaluating its prioritization strategy with the goal of increasing review capacity and predictability.

Before we move on, let's talk about amendments. Amendments are classified as either major or minor amendments as described in Section 1114.9 of the PMTA rule. FDA considers major amendments to be those that will require substantial FDA review time.

Examples of major amendments include substantial new data from a previously unreported study, detailed new analyses of previously submitted data, or substantial new manufacturing information.

When an applicant receives a major amendment, FDA would consider the applicant to have submitted a new PMTA, with the review period beginning on the date FDA receives the amendment. Therefore, under Section 1114.9(b)1, a new 180-day review period would begin on the date FDA receives a major amendment.

Minor amendments are any amendments that are not considered to be major amendments. They can be clarifications or other information that does not require substantial review time. Examples of minor amendments include administrative information or a

certificate of analysis.

Applicants can submit amendments at any time. Typically, if an amendment is received after the start of substantive review or Phase 3, Cycle 1, we will review the amendment in the next cycle.

If an amendment is received after the start of Phase 3, Cycle 2, it will trigger the major amendment review process, where the RHPM and Technical Project Lead, or TPL, review the amendment to determine if incorporating it into the review will require additional time.

If so, we reset the clock and adjust the due dates for the review team. Currently the major amendment process only applies to PMTAs and modified risk tobacco product applications, or MRTPAs, also known as MRs.

We will talk about other process changes next, but first I want to note that when an applicant submits a PMTA, we are focused on the receipt date. PMTAs received on the rule-effective date, or November 4, 2021, or later, are required to use FDA Form 4057a if an amendment is submitted.

This form is not required to amend pre-rule PMTAs, however, it is recommended so that we understand exactly what PMTA an applicant is trying to amend.

FDA can request additional information through a deficiency letter while the application is under review. This could be a major or a minor amendment.

If the applicant does not submit the amendment within the time period specified in FDA's request, FDA may, as described in Section 1114.9(c), consider the applicant to have submitted a request to voluntarily withdraw their PMTA.

FDA will then issue an acknowledge letter stating that the application has been withdrawn under Section 1114.11. Applications that have been withdrawn are considered closed and cannot be amended.

After review of the submission is complete and if Marketing Granted Orders are issued, we enter the post-market phase. CTP will generally specify any post-market reporting needs in the order

letter. These will vary based on the product and the submitted data. There are several submissions that applicants are required to submit.

An annual report is generally submitted and contains information from the previous year, including specimens of labeling, full-color advertising materials disseminated to consumers, description of each change made to manufacturing facilities or controls, inventory of ongoing and completed studies, description of the implementation of all advertising and marketing plans.

Summaries of the following: media tracking and optimization, analysis of the actual delivery of advertising impressions; analysis of all serious and unexpected adverse experiences, sales and distribution; implementation and effectiveness of policies and procedures regarding verification of age and identity of purchasers of products; all formative consumer research studies conducted; all consumer evaluation research studies conducted; creation and dissemination of the products' labeling, advertising, marketing, and/or promotional materials; and finally,

an overall assessment of how marketing of the tobacco product continues to be appropriate for the protection of public health.

Under Section 910(f) of the FD&C Act, we also require that applicants report to the FDA all adverse experiences that are both serious and unexpected and their analysis of the association between the adverse experience of each new tobacco product within 15 calendar days after the report is received.

These experiences may become known to an applicant through any source, including a customer's complaint, request, or suggestion made as a result of an adverse experience; a manufacturing deviation analysis; tobacco product defect; or a failure reported to the applicant or identified in the literature or media.

As part of post-market reporting, FDA has been requiring reporting for manufacturing deviations. Specifically, for products that have been distributed, if a manufacturing deviation occurs that the applicant determines a reasonable

probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in new tobacco products on the market that would cause serious adverse health consequences or death, the applicant is required to report the deviation to FDA within 15 calendar days of identification.

In addition to order -- in addition and orders, FDA has been specifying that under Sections 910(c)1(b) and Section 910(f) of the FD&C Act, applicants must submit certain notifications of their marketing plans and materials to FDA.

The requirement to submit the product's labeling, advertising, marketing, and promotional materials and plans in advance of their use is not for preapproval. That is, FDA is not requiring that it review and approve such materials or plans before they may be used.

Rather, such advanced notification will provide FDA timely access to such materials and plans and, if needed, allow FDA to provide advisory comments, including any concerns about their possible

impact on youth appeal and tobacco use initiation.

Applicants may begin disseminating the materials 30 days after providing notification to FDA.

Outside of required post-market reporting, an applicant may opt to submit additional stability data for their new -- for their tobacco product. Within their Marketing Granted Order, FDA has noted its findings with respect to the length of time the data in the application supports microbial and/or chemical stability of the product.

In some cases, applicants may not have had a completed study to support their contended shelf life and may not want to submit -- and may want to submit stability data for a longer period than originally submitted in the PMTA.

If an applicant received a Marketing Granted Order and would like to submit additional stability data for a longer period, FDA will review requests with data to support an extension. At the end of the review, FDA will provide notice to the applicant for what the new data supports.

Last, it is important to note that once a product is authorized by OS, the Office of Compliance and Enforcement will generally take the lead for post-market submissions. Both OS and OCE will monitor submissions and will triage to the appropriate party for review based on the information submitted.

Now that we have had an opportunity to discuss an overview of the statutory and regulatory requirements and the review process, I want to leave you with some resources which are available and may assist you as you navigate through the PMTA review process.

Here I have listed out some helpful resources CTP has provided for additional information. Our PMTA webpage includes important information and links to topics that will assist with PMTA preparation, metrics of PMTA review, as well as required forms and other content.

Thank you for your attention today during my presentation on premarket tobacco product applications. I understand there was a lot of

information discussed today, and I encourage you to ask questions during the panel discussion later on today, in addition to listening to the two additional PMTA presentations by Eric Cruz and Lauren DeBerry.

Thank you.

MR. CRUZ: Good morning, everyone. Thank you all for coming today. My name is Eric Cruz, and I'm a Regulatory Health Project Manager with CTP's Office of Science. I will be speaking to you all today about the program status on premarket tobacco product applications, otherwise known as PMTAs.

Outlined here you will see the agenda for this presentation. This presentation is meant to discuss more of our recent statutory and regulatory changes and then wrap up where we currently are with all of our PMTAs.

April 2022 brought out new statutory changes that significantly impacted the PMTA program, as well as products that are regulated by CTP.

The Consolidated Appropriations Act of 2022, which became effective April 14, 2022, amended the definition of the term "tobacco product" in

Section 201(rr) of the Federal Food, Drug, and Cosmetic Act, known as the FD&C Act, to include that contain nicotine from any source.

The Consolidated Appropriations Act also amended Section 901(b) of the FD&C Act, which concerns FDA's authority over tobacco products by adding a sentence stating Chapter 9 of the FD&C Act shall also apply to any tobacco products containing nicotine that is not made or derived from tobacco.

As a result, tobacco products that contain non-tobacco nicotine, known as NTN, including synthetic nicotine, are now subject to the provisions of Chapter 9 of the FD&C Act, including but not limited to, the adulteration and misbranding provisions, the required submission of ingredient listing and harmful -- sorry -- listing and reporting of harmful and potentially harmful constituents for all tobacco products, the required establishment, registration and product listing, the prohibition of selling tobacco products to individuals under 21 years of age, the requirement that new tobacco products have an FDA marketing order in effect, and

the requirement that modified-risk tobacco products have a modified risk order in effect.

As discussed in the Consolidated Appropriations Act, there was a period for submission of applications to market any tobacco product. As many tobacco products that contain a non-tobacco nicotine source were previously marketed, the law laid out a transition period for products being marketed in the United States within 30 days after enactment.

All such products were not considered to be in violation of Section 910 of the FD&C Act during a 60-day period following the enactment.

In order to market such a product after May 14, 2022, the applicant was required to submit a new PMTA under Section 910(b) of the FD&C Act within a 30-day period following the effective date. This period when -- where an applicant could submit to FDA was April 14, 2022 through May 14, 2022.

For the small number of applications submitted prior to April 14, 2022, they were submitted to FDA -- they were held by FDA until the effective

date of April 14, 2022. Rather than FDA refusing to accept, or RTA, the application, it was not reasonable for FDA to -- excuse me. It was not reasonable to RTA the application and request a new submission.

Therefore, FDA held the submitted application to review when the law became effective. If the applicant submitted a new PMTA in the 30-day period, they could continue to market that product during the 90-day period beginning the effective date.

Notably, a product with the tobacco-derived previous version that was subject to a refuse to file, or RTF, Marketing Denial Order, known as an MDO, or have been withdrawn could not continue to be marketed after the May 14, 2022, without receiving a Marketing Granting Order from FDA, as the transition period was only for NTN products.

During a short window of time, FDA received close to one million PMTAs by the May 14, 2022 submission deadline. Due to the transition period laid out in the Consolidated Appropriation Act, FDA prioritized reviews of these PMTAs.

One important point. As laid out in communications and our website, we have multiple ways for a submission to be received. For any physical submission, either paper, electronic, or hybrid, it had to be received by the CTP Document Control Center, known as DCC, before closing on May 14, 2022.

Any application received after the DCC closed was date-stamped the next business day. For applications submitted electronically, either utilizing the CTP portal or the electronic secure gateway, known as ESG, these have to be received by CTP DCC after the May 14, 2022, 11:59 p.m. deadline.

The time determined for receipt was based on the location of FDA, which falls under Eastern Time. The date for receipt for an electronic submission was not the date and time on the form. Instead, it was the date of receipt when submitted electronically through the CTP portal or ESG.

This is the same principle as dating a letter but physically mailing and receiving it at a later date. They may not match.

For applicants that wish to verify the

date and time of the receipt of their application, this is available for viewing in your CTP portal account. Or it can be provided by your assigned Regulatory Health Project Manager or RHPM.

For details on viewing content in your CTP portal account, we do have help with tutorials in our website and will have some related presentations later today as well. Additionally, many submissions were received after the deadline. As such, these were not prioritized.

Next, I will touch on regulatory changes that significantly impacted the PMTA program, including new requirements for complete applications. The PMTA rule was published on October 5 of 2021 and went into effect the same year on November 4.

The purpose of this rule was to improve the efficiency of the submission and review of PMTAs to help ensure that PMTAs contain sufficient information for FDA to determine whether a Marketing Granting Order should be issued for new tobacco products.

For this presentation, I will focus on

Subpart 1100 and 1114. Subpart 1100 includes general information such as the purpose and scope of the rule, definition, and recordkeeping requirements. Subpart 1114 includes information related to PMTAs, which will be discussed in more detail.

The PMTA rule requires applications to be submitted using certain forms provided by FDA, as described in Section 1114.7b of the 21 CFR. FDA Form 4057 and 4057b are required for a new PMTA, while FDA Form 4057a is required when submitting amendments or any general correspondence.

Failure to provide FDA forms 4057 or 4057b may result in a refuse-to-accept decision. Failure to provide FDA Form 4057a may result in information not considered during a review. More information on these forms will be provided in a later presentation. For reference, we've included a link in the slide that contains tips for completing the appropriate forms.

As noted earlier in the PMTA overview presentation, in the acceptance review phase, CTP reviews an application to ensure that products fall

under our jurisdiction and meet all statutory requirements for acceptance. With the implementation of the PMTA rule, additional criteria were added into the acceptance stage. Please refer to 21 CFR 1114.7 for the content.

These will be discussed in detail in the upcoming PMTA acceptance presentation later today.

Another change to the rule was how product information is ingested into CTP's system. Prior to the implemented rule, applications contained inconsistent information regarding the number of products, unique identification of each product, and were not clear which part of the application pertained to each product.

With the use of the required FDA Form 4057b, FDA is able to identify the products included in the application. Form 4057b serves as the authoritative source for what is being requested for review.

As such, RHPMs review this form for each PMTA to identify the total count of products as well as the unique identification for each product,

meaning the category, subcategory, manufacturer, name, package type, package size, characterizing flavor, as well as other properties as required by the PMTA rule.

In addition to the efficiencies gained from the use of these forms, FDA has taken strides to update systems we use to track and review each submission. We have moved from a completely paper-based system to one where our current -- where electronic submissions can now process and load content directly from our forms.

One example of efficiencies gained is our ability to automatically ingest product information directly from FDA Form 4057b into our systems. Upcoming presentations will cover content required as well as a new tool available to assist industry in ensuring completion of forms is consistent with our system needs for ingestion.

As discussed previously today in the PMTA overview presentation, the purpose of a filing review is to determine if the application contains the necessary information to initiate substantive review.

With the PMTA rule, applications have specific requirements for filing that fall under multiple disciplines. These criteria can be found in 21 CFR 1114.7.

With the addition of these requirements, there's gained efficiency in decision-making, as now we can issue a refuse-to-file, or RTF decision for those applications missing basic content which is needed for a full review.

For example, if an application contains three clinical studies but only a summary is provided, there is no line listing data for our scientists to perform their own independent assessment. As such, the application would receive a refuse-to-file decision.

Now with the PMTA rule in effect, applications require all labeling specimens for filing that are specific to a corresponding new product. The labeling specimens must be accurate, accurate to the actual size and color, and include relevant warning statements. More information about labels can be found at 21 CFR 1114.7f.

We have provided an image here of a generic label that would be acceptable for filing. Notice it only contains one panel and does not contain accurate information that is proposed to appear on the labels.

This slide was shown earlier today in the PMTA overview presentation. You can see in this second section of the slide in the blue color many filing requirements were added to the PMTA rule. This additional information is cumulative, meaning applications may meet the -- may need to meet the requirements in both sections.

As you can see, applications are required to -- applicants are required to submit more information now than prior to the rule. With these new requirements in place, we increase the number of disciplines assigned to review relevant content at the filing stage.

The filing team consists of chemists, engineers, microbiologists, toxicologists, medical officers, behavioral pharmacologists, social scientists, epidemiologists, staff from the Office of

Compliance and Enforcement, project managers, and a technical project lead, or TPL.

Also, the filing team is looking to ensure all content necessary for substantive review is present. It is no longer just a review for presence or absence of material. Instead, our review team is looking to ensure all summaries, line listing protocols, references, process flows, testing methods, etc., are included.

Additionally, the expectation is that the application is complete. If required information is missing, or if a statement was provided that additional information would be provided later, the application will likely receive a refuse-to-file decision.

Lastly, I want to make two additional notes. Most of the environmental considerations are now considered during the acceptance phase. For example, lack of an environmental assessment would result in a refuse-to-accept decision.

Please note, we are still assessing tobacco product samples in Phase 3 of the substantive

review phase. As such, samples -- if samples are needed, FDA will send a letter to the applicant. This letter will provide information on the exact number of samples to be sent, the location to send samples to, as well as a date this must be completed by.

We have found this procedure reduces burden for both applicants and FDA and ensures samples are quickly processed upon receipt. Although this may occur in the scientific review phase, applicants should be ready to submit samples at any time once they have had their application accepted by FDA.

For completeness, I want to touch on changes in the substantive review phase. In short, there is no change to the standard we use to issue a Marketing Granting Order. Additionally, earlier -- the earlier PMTA overview presentation provided some procedural changes, such as issuance of no more than one deficiency letter in a 90-day response timeframe.

With a large number of applications, it was critical to ensure consistency and review approach across applications. Deficiency language for each discipline was reviewed, edited, and

expanded to accommodate new product categories. TPLs were provided a lead TPL to assist with approach, communication, and interpretation of a totality of the data.

Additionally, the senior leadership team in the Office of Science regularly met with each TPL to ensure complex issues were discussed and the review team conclusions were consistent with emerging science. FDA continues to prioritize applications which will facilitate the transition from our current marketplace to a fully regulated marketplace.

However, during this time, hard deadlines were imposed from other sources. Understanding the Consolidated Appropriation Act had a transition period which required decisions, FDA prioritized applications that were submitted within the 30-day window. Additionally, FDA is prioritizing the review of applications related to the litigation brought on by the American Academy of Pediatrics.

And now I want to share where we currently are with the PMTAs that have been received to date. As of the end of fiscal year 2023, or September 30,

2023, FDA has received a total of 26,604,609 PMTAs, and closed a total of 26,042,715 PMTAs.

Of the over 26 million applications received, CTP has completed the acceptance phase and issued decisions on approximately 99%, with over 6 million acceptance decisions and over 19 million RTA decisions. Of the over 6 million applications accepted, CTP has completed the filing phase and issued decisions on approximately 94%, with over one million filing decisions and over 5 million RTF decisions.

CTP has completed the scientific review phase and issued decisions on a large number of applications, with 45 Marketing Granting Orders and over one million Marketing Denial Orders.

In total, CTP has closed approximately 98% of all PMTAs received. As of the end of fiscal year 2023, approximately 2%, or 561,894 PMTAs remain pending.

As of the end of fiscal year 2023, FDA wanted to provide progress on the products included within the NTN bolus. This includes applications

submitted April 14, 2022, through May 14, 2022. Of the more than 900 applications received, CTP has closed 926,346, or approximately 99%.

All applications have completed the acceptance phase and either received an acceptance or RTA letter. For the one percent of applications remaining, they will continue to move through the review process. These applications were prioritized due to the transition period previously discussed.

As the agency moves forward with PMTA review, FDA will continue to prioritize applications. We are focused on transitioning the current marketplace to a fully regulated marketplace. FDA will continue to prioritize products that have a significant impact, such as those that have a large presence in the marketplace.

FDA is committed to sharing the progress of application review and decision-making through various mechanisms. This public meeting is one example of the different means of communications. We will also continue to utilize traditional sources, such as web updates, tweets, conferences, etc.

While significant progress has been made in the review of applications, the agency will continue to explore efficiencies and provide updates to applicants and the public have predictability for when a decision will be provided.

And finally, FDA will continue to ensure each application decision is supported by the current science and that the data to support the decision is specific to the product.

Thank you all very much for your attention today. If you have any questions after this presentation, I encourage you all to ask them during the panel discussion today. You may also contact either the call center, our Office of Small Business and the Office of Small Investment or send an email to askCTP@fda.hhs.gov.

Thank you.

CDR RUSSELL: Thank you, Eric and Huda.

Before we actually break for a short 15-minute break, I would like to announce that there is a little convenience store within the lobby for you guys to purchase any beverages, snacks that you may

need.

We also would like to make sure that you utilize the index cards to write any questions that you may have for the second panel session.

We will break for a 15-minute break, and we will reconvene approximately at 10:16. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:01 a.m. and resumed at 10:26 a.m.)

CDR RUSSELL: Welcome back, everyone. I hope everyone has had the opportunity to get your beverage of choice, stretch your legs, socialize and get a chance to just talk to FDA staff and colleagues that you have not probably seen in a very long time.

We'll get right back into our presentation, and we'll start with Section 2, the required content and format of PMTA submissions. Presenting first will be Ms. Lauren DeBerry to discuss PMTA acceptance, followed by Sequoia Bacon, discussing tobacco master files, followed by Chrissie Cai to discuss data standards. Welcome, Lauren.

MS. DeBerry: Good morning, everyone. My

name is Lauren DeBerry, and I'm a senior regulatory health project manager in the Office of Science. Today I'm going to talk to you about PMTA acceptance.

We will discuss PMTA forms, acceptance questions and common issues that have led to RTAs.

As discussed earlier in the PMTA overview presentation, on October 25, 2021, FDA issued a final rule to set requirements related to content, format and procedures for PMTAs.

The rule helps to ensure that PMTAs contain sufficient information for a valuation such as details regarding the physical aspects of the product and information related to the product's potential public health benefits and harms.

This went into effect for all PMTA applications received November 4, 2021 or later. The focus of my presentation today is on lessons learned around acceptance.

To start, one major change with the PMTA rule is the requirement of forms. 21 CFR 1114.7(B) provides the requirement that each PMTA must contain forms. If a required form is missing, this is a basis

for a refuse to accept decision.

The information in each required form is the authoritative source for that data. For example, if a submission contains 20 products in FDA Form 4057b, but the cover letter identifies 50 products, FDA intends to only review the 20 products that are identified within FDA Form 4057b. The remaining products will be considered failing to include required forms.

Prior to the PMTA rule, many applications were inconsistent in the number of products provided for review as well as their unique identification information.

FDA saw differences in cover letters, labels, products identified in Module 3, the composition module, as well as products listed in the environmental assessments. Additionally, the products were not consistently identified, so it was difficult to identify the differences.

With the use of the form, the form is the one source where the applicant identifies what is to be reviewed. Therefore, it is important to ensure

that your forms are correct and that the application is consistent with what you have provided in the form.

That was discussed -- what forms are required for PMTA. FDA forms are developed to allow for efficient processing and reviewing of applications. Currently, there are three required forms for PMTA submissions.

FDA Form 4057, Premarket Tobacco Product Application Submission Form is required for all PMTA applications received November 4, 2021 or later. This form collects information in sections such as applicant, manufacturer information and certifications.

FDA Form 4057a, Premarket Tobacco Product Application Amendment and General Correspondence Submission Form is required when sending in amendments for PMTAs or when submitting general correspondence such as adding new points of contact to your submissions or to request transfer of ownership of a submission to a new company.

We encourage applicants to submit complete applications and therefore do not require

this form at acceptance. However, if an applicant amends an application prior to acceptance, this form and all the information in the required sections must be included for us to include the submission in our review.

FDA Form 4057b, Premarket Tobacco Product Application Proofing Product Submission Spreadsheet, also referred to as the Unique Identifying Information for New Tobacco Products Spreadsheet, allows for applicants to organize their new product identifying information by category and subcategory.

Use Form 4057b for all PMTA submission types. You will hear more about Form 4057b in a later presentation.

21 CFR 1114.7(C) requires 12 main information to be provided within the form. You don't need to try to read all of this. This slide is here for your later reference. I am going to walk through the form and identify where each of these requirements should be provided.

Please note, I am going to go in the order of the form, not the order you see here. FDA Form

4057 contains all of the required information listed here, except for Items 3, Parts 2 and 3. FDA Form 4057b is where unique identification information for the product is provided.

Here is the snapshot of the revised 4057. All content from this form has been previously maintained, meaning our updates are included in the same sections as what were in before. However, we have updated the organization and provided additional instructions for clarity.

To provide the required information for applicant name, address and contact information, Section 1, Part A, must be populated. This section should be completed as either an organization or an individual, not both.

If the applicant is an organization, Fields 1 through 20 should be populated, and Fields 21 through 36 should be left blank. If the applicant is an individual, Fields 21 through 36 should be populated, and Fields 1 through 20 should be left blank.

To provide the required information of

authorized representative or U.S. agent for foreign applicants, include the name, address and contact information in Section 1, Part B.

Remember that an authorized representative or U.S. agent is the responsible official that can act on behalf of the applicant.

This is different than a contact. An authorized representative or U.S. agent can submit an amendment, withdraw applications and make decisions. In contrast, a contact is an individual authorized to speak with FDA, but they do not have the authority to make decisions, submit or remove content for an application.

To reduce data entry, if the authorized representative or U.S. agent is the same as the applicant identified in Part A, you can check the box and skip the remaining fields in Part B. If the authorized representative or U.S. agent is different than who was identified in Part A, you need to select which party you are identifying, authorized agent or U.S. representative, and provide the information in Fields 3 through 18.

If the authorized representative -- pardon me -- it is important to remember that for every foreign applicant, the U.S. agent is required. The U.S. agent is defined as a responsible official who either resides or maintains a place of business in the U.S. and who is authorized to represent the foreign applicant.

Highlighted on the screen here, you will see Part C, alternate point of contact information. This is optional but should be used if there are additional applicants, authorized representatives, U.S. agents or other contacts that have not been previously identified in the form.

For each additional party, a unique Part C should be completed, meaning if you are adding two additional authorized representatives, then two Part C sections should be populated with all the information as required.

Note here, the blue button is a continuation button. It's on the bottom right of the form. This button will take you to a continuation appendix where additional context can be added. This

button has been added throughout the form to assist applicants.

To provide the required information from manufacturer address and facility's establishment identifier numbers, also known as FEI numbers, of the establishment involved in manufacture of the new tobacco product, populate Section 1, Parts D and E.

To reduce data entry if the manufacturer is the same as the applicant identified in Part A, you can check the first box and skip the remaining fields in Part D. However, if the manufacturer is different than who is identified in Part A, you will need to populate the information in Part D, Fields 2 through 20.

You will also see another part on your screen, Part E, manufacturer of packaging sterilization sites. This is optional, but should be used if there are additional manufacturing sites that were not previously provided in Parts A or D.

For each unique site, populate a separate section for Part E, meaning if there are two additional packing sites, then two Part E sections

should be populated to provide the needed information.

Section 3, Parts A through C, of FDA Form 4057 identifies the type of PMTA, the dates of any previous marketing in the United States as well as provides the ability to cross-reference information.

When selecting the submission type, remember a standard PMTA is a submission from an applicant seeking a marketing granted order to introduce the new tobacco product into interstate commerce.

A resubmission PMTA is submitted to seek a marketing grant order for a new tobacco product providing new information to address deficiencies outlined in the marketing denial order cross-referencing the content from the denied PMTA.

A supplemental PMTA is submitted by an applicant seeking authorization for modifications made to a new tobacco product for which they have already received a marketing granted order.

Complete Part B if the application has one or more cross-reference to another PMTA or MRTPA

as allowed under 21 CFR 1114.7b, .15b and .17b. Supplemental PMTAs and resubmissions may cross-reference content in standard PMTAs. Standard PMTAs should not cross-reference another standard PMTA or other pending applications. Within the table, use the single row for each cross-reference.

Complete Part C if the application includes a reference to a tobacco product master file also known as a TPMF. When provided the information for each TPMF, it is important to provide as much detail as possible.

There may be cases where an applicant may not have received access to the TPMF submission tracking number or STN. This could be due to a recent TPMF submission where the STN is not known yet or the information has not been provided by the TPMF owner.

In these cases, the TPMF owner name as well as the date of the TPMF submission are helpful for FDA review. Although the form does not include a space to capture the date of the submission, this can be included within the right of reference.

Please remember, a right of reference for

each TPMF referenced is required for acceptance. The form has a field for the applicant to indicate the inclusion of the right of reference. FDA will verify the inclusion of this right of reference for each TPMF. Lack of this information may result in a refuse to accept decision.

Section 3, Part D, of FDA Form 4057 identifies any formal meetings held with FDA related to the new products. Complete Part D if FDA and the applicant held one or more meetings related to the new products.

This may include meetings held to discuss study designs, earlier versions of the products or other topics. Within this table, use a single row for each meeting.

Section 4 of FDA Form 4057 is intended to help applicants organize their submission. For each item included in your submission, select the corresponding check box in the list and provide the location of the documents, such as the file name or the document name and page number.

Part A captures the request to have the

PMTA referred to TPSAC. To request this referral, check the box and provide the location within the application where you request the referral and your rationale. As a reminder, FDA will make the final decision on whether a PMTA is referred to TPSAC.

For all the enclosures, check the appropriate box and provide the location of the file. FDA generally expects product samples to be required as a part of the PMTA submission and that an applicant should be prepared to submit them in accordance with FDA instructions.

There may be situations where samples may not be necessary such as PMTAs that are submitted as a part of a submission where you are looking to address deficiencies of a previous marketing denial order, such as a resubmission, or PMTAs submitted for modifications to an authorized product or the modifications do not require new samples as a part of the PMTA evaluation process.

Pre-submission meetings with FDA may help to provide additional information about whether product samples will be needed for your PMTA.

However, in most situations, FDA will not be able to determine the need for product samples until after PMTA has been accepted.

Section 5 of FDA Form 4057 should be filled out to provide a brief statement regarding how the PMTA satisfies the content requirements of Section 910(b)(1) of the Federal Food, Drug and Cosmetic Act and a brief description of how marketing the new product would be appropriate for the protection of public health.

When discussing how the PMTA satisfies the content requirements, your description should include the following information at a high level. Report all information published, known or should be reasonably known to the applicant concerning investigations to show the health risks of the product and whether the product possesses less risk than other tobacco products, a statement of components, ingredients, additives, properties and the principles of operations of the product, a description of the methods, the facilities and controls used for manufacture, a statement identifying any product

standards under Section 907 applicable to any aspect of the tobacco product and either adequate information to show the product fully meets that product standard or adequate information to justify any deviation from that standard, a description of a labeling proposed for the new product and other information relevant to the subject matter of the application as the Secretary may require.

As noted earlier in my presentation there are 12 main items that are required to be provided within the form. Most of them are provided within FDA Form 4057. However, FDA Form 4057b is used to provide the unique identification information for the new product.

Form 4057b is an Excel spreadsheet with three different tabs: instructions, introduction and product. Here you see the introduction tab, where you can insert the applicant name, which should match what was provided in Part A of FDA Form 4057, the product category such as ENDS, cigars or smokeless, the product subcategory and the application type.

Please pay particular attention to the

instructions for this form as improper data entry may result in the inability for FDA to ingest your applications. This will be covered in a later presentation.

Once you have populated your fields for the introduction tab, click on the enter unique properties button to proceed with the product tab.

FDA Form 4057b will identify which unique identifies are needed by product category and subcategory. If an applicant is submitting a group submission with products in multiple categories or subcategories, a new 4057b will be needed for each.

Here is an example of the product tab for an ENDS closed e-liquid. You will notice by clicking on the enter unique product properties button, the fields have been altered to provide the required properties needed for acceptance. Applicants can then proceed with populating information in each row for a unique product.

It is important to remember that FDA Form 4057b can only hold up to 5,000 products. Therefore, if you have more than 5,000 products within your

application, you will need multiple forms. For example, if you are submitting 12,000 products, you will be required to submit at least three FDA Form 4057b forms.

Now I want to spend a few minutes to explain some important sections related to the PMTA forms. Although not required to be provided within the form by the PMTA rule, applicants can conveniently find certification statements in Section 6 of FDA Form 4057.

Certifications are required for acceptance. However, they can be provided in the form or separately within your PMTA. To facilitate accurate submission of certification statements, FDA has provided FDA Form 4057 with five different certifications for use.

Certifications 1 through 4 are based on the type of PMTA you are submitting. As such, only one of the four should be included. Certification 5, Financial Interests and Arrangements of Clinical Investigation Certification Statement, should be used for any PMTA type that includes any study in support

of the application. This certification covers all actions taken to ensure the reliability of the studies.

A certification statement for standard PMTAs is appropriate when submitting standard PMTAs. When populating the fields for the certification statement, ensure that the name used for the authorized representative is the same as the name of the authorized representative identified in Section 1 of FDA Form 4057, and the name of the organization should match the name you identified in the form.

The modified tobacco product certifications for supplemental PMTAs are appropriate when submitting a supplemental PMTA. Again, when populating the fields for this certification, ensure the name used for your authorized representative and organization match what was provided previously in FDA Form 4057.

Additionally, there are fields to identify product names. These names should match the names used in FDA Form 4057b. And as with the submission for modifying a previous PMTA, you will

need to provide a description of each modification and the STN of the previously submitted PMTA. If submitting for multiple products, it is recommended to submit a separate certification statement for each supplemental PMTA.

The same product certification statement for resubmission is appropriate when submitting a resubmission PMTA where the product is unchanged, and the applicant is addressing deficiencies outlined in the marketing denial order or MDO.

When populating the fields for this certification, ensure that the names of your authorized representative and your organization match and that the identified information matches what was previously put in FDA Form 4057.

Additionally, there are fields to identify product names. These names should match what was provided in FDA Form 4057b.

You must also provide the STNs of the previously submitted PMTAs that received an MDO. The different product certification for resubmissions is appropriate when submitting a resubmission PMTA where

the product modifications have been created to address deficiencies that were in the MDO. This means that the physical product is different than the product that received the denial.

When populating the fields for this certification, ensure the name used for the authorized representative and the organization match what was identified in Form 4057. The product name should match what was identified in 4057b.

And similar to the modified tobacco product certification, the modifications that you have made will need to be provided within the certification as well as the STNs of the products that previously received the marketing denial order.

Again, if you are submitting for multiple products, it is recommended that you provide a separate certification statement for each resubmission.

Although not required for acceptance, I would like to discuss FDA Form 4057a, Premarket Tobacco Product Application Amendment and general correspondence submissions.

You must include FDA Form 4057a if you are amending a PMTA, populating Section 3 of the form. You will need to indicate it is an amendment by checking the box. You will also need to provide the STN of the PMTA you are amending.

If this is not populated, there is no linkage as FDA cannot infer which submission this is associated with. If you fail to provide the STN, the amendment will not be reviewed. If you are unsure of what the original PMTA's STN is, you have several options.

You can look at your acceptance letter, which lists the STN. You can look through CTP portal, or, if you have not received the letter and the STN is not viewable in CTP portal, you can contact your assigned regulatory health project manager.

And remember, select the amendment response type. If the amendment is in response to a deficiency letter, be sure to include the date of the FDA letter in month, day and year format. If the amendment is in response to another type of letter, check other and include the date of the FDA letter.

For more information about filling out 4057a, you can refer to the amendments tips completing Form FDA 4057a fact sheet, which is available on our website. The fact sheet has tips for each section of the form and a link to a video to help applicants find their STNs in CTP portal.

All required forms are available on the FDA website. As seen here, you can filter the page to display only the forms for CTP. When preparing an application, we recommend that applicants always get a new copy of the form from the website to ensure that they are using the latest version of the form. This is important as forms can be updated with new content. If an old form is utilized, it may be missing information necessary for acceptance.

If you are having trouble navigating the main FDA forms page, there is an alternative location to find the PMTA forms. FDA Forms 4057, 4057a and 4057b are linked on the Premarket Tobacco Product Application page under the preparing a PMTA section.

Now that I have gone over the forms, let's talk about acceptance requirements not captured in

4057 or 4057b. Here you see the acceptance requirements for PMTAs. The first two sections are those that were applied to all PMTAs received prior to November 4, 2021.

Those requirements remain unchanged. Applications received after the final PMTA rule must meet those criteria as well as the new criteria in the rule. I now will provide detail for the remaining requirements not already addressed and captured in the FDA forms.

To be accepted, the products must be within CTP's jurisdiction, meaning the products are tobacco products and not food, drug, devices or combination products.

As mentioned in the PMTA status presentation, FDA now has jurisdiction with products that have nicotine derived from any source. As such, products with nicotine from any source are now subject to FDA regulation and will require an application.

To be accepted, applications must meet the following format requirements. Applications must be submitted in an electronic format that FDA can

process, read, review and archive. If for some reason, an applicant is unable to submit electronically, they must request a waiver to submit in non-electronic format in advance of their submission, and they should include that waiver in their application.

Applications must contain a comprehensive index in the Table of Contents. All sections of the application must be in English or provide translations of all sections that are not in English.

If including translated documents, the following translation requirements must be met. Applications must include the original language version and non-English information must be translated into English.

Applications must contain a signed certification statement signed by an authorized representative certifying that the English translation is complete and accurate.

Applications must contain a brief statement of the qualifications of the person who made the translations.

Applications must contain a concise description of the new tobacco products and documents describing the plan to market the tobacco products.

Applications must contain labels for each new tobacco product or provide a representative label that clearly indicates which information changes in the label with placeholders.

If the brand is identified on the label, the applicant then must provide an example label for each brand. If the new products are subject to product standards issued under 907 of the FD&C Act, those applications must also contain a statement identifying all tobacco product standards that are applicable to the new product and a brief description of how the new product fully meets the identified standards.

Applications must contain an adequate environmental assessment under 21 CFR 25.40 or a valid claim of categorical exclusion under 21 CFR 25.35.

The only valid categorical exclusion for tobacco products are for SEA reports that are provisionals or negative actions. All other

marketing applications are required to have environmental assessments. So let's focus on how to submit an adequate environmental assessment.

The EA must include the environmental impacts related to the use of the product and the environmental impacts related to disposal of use of the product. These are the A requirements for acceptance. Additional elements of the applicant's EA will be reviewed in later review phases.

For more information about preparing an EA, you can refer to the National Environmental Policy Act Environmental Assessment for Tobacco Products Categorical Exclusions Guidance available on our website.

As both applicants and CTP have gained experience and PMTA acceptance, we have found the following to be common reasons for RTAs.

Lack of required forms. Remember that FDA Forms 4057 and 4057b are required for acceptance. Please make sure you are using the latest version of the form by checking FDA's website.

Lack of adequate EA. EAs should be

product-specific and include information on the impact of use and disposal of use for those products.

Lack of right of reference for applications referencing TPMFs. Use the check box in the form as a reminder to check that you included the right of reference.

Inadequate English translation. If applications contain translations, you must include a signed certification statement by an authorized representative certifying that the English translations are complete and accurate and a brief statement of the qualifications of the person who made those translations.

Here are some helpful reminders about submitting PMTAs. Prior to submitting to FDA, ensure that you are using the most updated version of the forms by checking our website and ensure that all information in the form in the required sections is readable after saving.

We recommend saving FDA Forms 4057 and 4057a using save or save as in Adobe. This allows CTP to access information saved in dynamic fields,

meaning CTP can access text beyond the visible defined box. We recommend submitting FDA Form 4057b as an .xls or .xlsx file rather than a PDF.

Verify your submission meets FDA's technical requirements. Please refer to the revised electronic submission file formats and specifications document available on FDA's website for more information.

If submitting via CTP portal, the name used on Form 4057 must exactly match the name provided and associated with your CTP portal account.

If they do not match, CTP will not be able to display the submission or provide the submission STN number within the submissions or notification tab in your portal account.

Best practice is to use the legal business name as listed in Dun & Bradstreet for both your portal account and your applications.

When providing product names throughout your application, please ensure that the name is consistent with what you have listed in FDA Form 4057b.

If there are inconsistencies, FDA will use the name identified in 4057b. If your product has multiple names, please include the additional names in the additional property section in the form.

Download and use the new FDA 4057 validator tool. This tool verifies the content in your form meets required formats and CTP can adjust it. You will learn more about this later this afternoon.

That concludes my presentation. As a reminder, this was focused on PMTA acceptance. Applications that are accepted then undergo filing review.

In closing, I encourage you to review the final PMTA rule for more information on how to prepare an application that will successfully meet the filing requirements and for more information about PMTA applications in general.

MS. BACON: Good morning. My name is Sequoia Bacon, and I am a regulatory health project manager in the Center of Tobacco Products, Office of Science.

Today my presentation will focus on tobacco product master files, also known as TPMF. This presentation will cover the following topics. A brief overview of the TPMF, methods on providing another party the right to reference the TPMF, TPMF process, the types of FDA letters TPMF owners may receive following our scientific review, and conclude with a TPMF closer process.

Let's start with an overview of a TPMF. Certain submissions may require applications to provide trade secret and/or commercial confidential information such as ingredients or test methods that are owned by a third-party.

A TPMF is a file voluntarily submitted to CTP that contains information about a tobacco product or component that the TPMF owner does not want to share with other persons. This can be beneficial, too, for manufacturers, component or ingredient suppliers, and researchers to streamline the tobacco products submission process for both CTP and applicants.

So how does a TPMF work? Simply, a TPMF

owner grants an authorized party the right to reference the TPMF in support of a tobacco product submission to CTP.

CTP can then access and review the confidential information as part of our review of that submission. At no point in time does the authorized party see or have access to the confidential information. Additionally, to preserve the confidentiality of all trade secret or confidential information, FDA communicates review findings separately from the TPMF owner.

For FDA to review a TPMF, if a party other than the TPMF owner seeks to reference a TPMF, that party must have appropriate authorization or right of reference.

Let's walk through this process. TPMF owners or their authorized representatives can grant a right of reference in many ways, such as through a letter of authorization, also known as an LOA, provide a listing of authorized parties directly within the TPMF or through other written documentation such as a contract between the TPMF owner and applicant.

And an important note, the PMTA final rule requires applicants using a TPMF to first provide documentation that their right of reference to the master file and clearly identify the specific context incorporated in the PMTA.

FDA evaluates whether a PMTA meets this requirement during the acceptance phase of the PMTA, which was covered in today's earlier presentations. LOAs are a common method of providing the right of reference. So I will discuss in more detail on how both the TPMF owner and an applicant can prepare and submit an LOA.

For FDA to determine that an LOA provides sufficient information, we recommend the following information. First, the LOA is provided on the TPMF owner's letterhead. Second, it provides the contact information of TPMF owner, and then thirdly it clearly identifies the documentation as an LOA. And lastly, if known, the submission tracking number or STN of the TPMF should be provided.

In the red box is the name of the company authorized to reference the TPMF, including their

contact information. It is important that the authorization is specific to the company that is authorized.

An LOA would not be a valid right of reference if the PMTA, for example, is submitted by Company A but the LOA identifies Company B.

In the yellow box, the TPMF owner provides any limitations on the authorization. For example, if the TPMF owner is authorizing others to use only certain sections of the TPMF and, if so, would identify those sections. In this case, there are no limitations to the authorization.

In the blue box is the signature of the TPMF owner. An LOA would not be a valid right of reference if it lacks a signature of the TPMF owner or an authorized representative. As a best practice, the TPMF owner should provide the original LOA to FDA as an amendment to their TPMF and provide a copy of the LOA to the applicant.

Again, to meet the PMTA requirements, the applicant must include the right to reference documentation in their PMTA, and this copy of the LOA

will suffice for this purpose.

Now we will look at an example of this process. Company A intends to submit a PMTA for an ENDS product. Company A utilizes a complex flavor purchased from Company B and their e-liquid.

For the PMTA, it is necessary to provide the full ingredient information among other items for the ENDS product. However, Company B does not want to provide that information to Company A.

Instead, Company B can establish a TPMF that includes all of the complex flavor information. Company B provides CTP an LOA as an amendment to the TPMF that grants Company A the right to reference the TPMF.

Company B also provides a copy of an LOA to Company A. Now Company A can submit a PMTA and CTP can review on behalf of the Company A the complex flavor ingredient materials and manufacturing information located in the TPMF. This benefits Company A to ensure a complete application and benefits Company B by allowing use of their complex flavor information without disclosing trade secret

information to Company A.

Now I will explain how FDA processes TPMFs. There are three processes that occur over the life cycle of a TPMF. First is the establishment process. This is the stage when CTP determines whether to establish a new TPMF in response to requests from the owner of the confidential information, such as a manufacturer, component supplier, ingredient supplier, or researcher.

Second is a scientific review process. This is the stage when a submission references a TPMF. At this point, CTP determines if scientific -- performs a scientific review and ends with a determination of whether a TPMF is sufficient for FDA to make a scientific finding on the referenced submission.

And lastly, the closer process, this is the stage when a TPMF owner may choose to close its TPMF or CTP and may initiate closure of TPMF if within three years it either has not been referenced or there have been no updates made to the TPMF.

Now a last look at each step in more

detail. Let's begin with a TPMF establishment process. Upon receipt of a new request to establish a TPMF, CTP will review the submission to ensure it contains enough information to establish a TPMF. CTP will establish a TPMF based on the guidance released in May 2016 which can be accessed on the FDA website that contains the following information.

It includes a cover letter with specific information that supports a tobacco product currently regulated by CTP and table of contents.

The submission contains a clear statement of intention to establish a TPMF with CTP and identifies the TPMF owner. The submission contains sufficient contact information including the address and phone number for the TPMF owner or authorized representatives.

Additionally, your TPMF request should contain the signature of the TPMF owner. Currently, this can be electronic or a physical signature. When your request is submitted by a person other than a TPMF owner, such as a representative, include written documentation from the TPMF owner granting the

representative authorization. It is also helpful to clarify if the authorized representative may also grant rights of reference to the TPMF.

If the TPMF owner is a foreign entity, we encourage providing an authorized representative who either resides in or has a place of business in the U.S.

Also, if submitting electronically, FDA will need to process, read, review and archive the content. For example, we encourage files not to be password protected.

And lastly, we encourage documents to be provided in English, and if portions are not in English, provide a complete English translation of this content.

When all information is present, CTP issues an acknowledgment letter to the owner confirming their receipt and establishment. The letter identifies the owner. CTP assigns STN contact information for the regulatory health project manager and information on how to update the TPMF.

If additional information is needed for

establishment, CTP will contact the owner. We intend to work with the submitter to ensure all requested information is received. Receiving an acknowledgment letter means that the TPMF is established and now is ready for scientific review.

So many of you may be wondering: what does the content within a TPMF undergo scientific review? Consistent with other FDA centers, CTP does not intend to conduct a scientific review of a TPMF at the time of establishment. Instead, CTP will begin a review only when the TPMF is referenced in an authorized party submission.

Also, the scope of the TPMF review would be limited to the information that was cross-referenced. In the case of the previous example, Company B's TPMA may contain ingredient information from multiple complex flavors. However, CTP would only review the specific complex flavor or flavors that are cross-referenced in Company A's PMTA.

The following slides will examine the process for reviewing a TPMF that is referenced in a PMTA.

Scientific review of a TPMF and the PMTA is done concurrently. If the PMTA is not accepted and filed, scientific review does not occur for either the TPMF or the PMTA. In keeping with our complex flavors TPMF example, once Company A's PMTA has been accepted and filed by CTP, it will enter the scientific review process. As part of scientific review, CTP will again review the right of reference to ensure it remains valid.

As an example, the LOA will no longer be valid if it was revoked by the TPMF owner or if the TPMF has been closed. Additionally, CTP will review any limitations on the authorization. For example, is Company A authorized to reference certain sections of the TPMF or only specific flavors? If Company A does not have authorization, CTP will not review the TPMF. If the right of reference is valid, CTP begins review of both the application and TPMF.

Again, CTP will limit the scope of the TPMF review to only the information that is authorized by the TPMF owner.

This review will result in CTP

determining if the information in the master file is adequate or inadequate for the PMTA referencing it.

Let's presume CTP determines that TPMF content is adequate. This means there is enough information present for CTP to make a scientific finding on the cross-referenced application. Based on this, CTP does not need to request additional information from the TPMF owner.

There is one thing to consider. Even if the TPMF does not have deficiencies, the same may not hold true for the referencing application. There could be application deficiencies outside of the scope of the TPMF review.

If deficiencies are found within the TPMF, at the end of scientific review, CTP will issue either a deficiency letter or an advice information request letter.

Here is a comparison of the letters. Deficiency letters are separately issued to the TPMF owner and the applicant to request information that is required for us to make a scientific finding on the referenced submission.

The applicant will receive a deficiency letter that will provide details for application specific deficiencies and additionally include a general statement that we have identified issues in the TPMF. No details of the TPMF deficiency will be provided to the applicant. The TPMF owner will receive their own deficiency letter that will provide specific details on the deficiencies within the TPMF.

The response time will be the same for both the applicant and the TPMF owner. Advice information letters, or AI letters, will be issued to the TPMF owner only when a final decision is issued to the referencing application, but a deficiency still exists under the TPMF and when the FDA is conveying deficiencies as a notification only.

A response time is not provided in the AI letter. So, we encourage the TPMF owner to update their information in the master file if the information will be referenced in the future.

It is important to note that the applicant is solely responsible for ensuring that their Premarket Application and supporting documents,

which will be the TPMF in this case, are adequate to support the appropriate premarket standard for marketing authorization.

If the TPMF owner does not respond or fails to provide a complete response, this may impact the referencing submission. Therefore, we encourage our applicants and TPMF owners to communicate and coordinate their responses to deficiency letters to adequately address the identified issues in requested time frame.

So far, we have discussed the establishment and scientific reviews of a TPMF. Now we will discuss the closure process, which may be initiated by either the TPMF owner or CTP.

TPMF can be closed by a request from the owner. The owner should submit a closure request in writing and include the reasons for requesting closure of the file and the date the TPMF should be closed.

The owner is recommended to notify all persons currently authorized to reference the TPMF of the closure. Once closed, the TPMF can no longer be

referenced or reviewed by CTP.

TPMF can also be closed by FDA initiation. FDA will initiate closure process when a TPMF has not been referenced within three years of the date of its establishment or the owner has not submitted an update.

Prior to initiating closure of a TPMF, a notification letter to the owner will be issued. If the owner fails to respond to the notification letter within the requested time frame, CTP will issue a pre-closure letter to keep the TPMF active. If still no response, CTP will issue a closure letter.

Please note that if a TPMF is closed and a company determines one is still required, the company can submit a new request to establish a TPMF. Once closed, a TPMF will no longer be available for reference.

This concludes my presentation. I understand that there was a lot of material to consider. If you have questions after this presentation, I encourage you to ask them during the panel discussion. You may also contact a regulatory

health project manager. Their name and contact number is located at the bottom of your letters.

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

CMDR. RUSSELL: Before we have our next presentation, we are receiving several questions. And we just want to make a reminder to keep your questions to the scope of the meeting.

If your questions are submitted and they are outside the scope of the meeting, they will not be addressed in the panel on the second day. However, they will be addressed separately via email. Please send any questions that you do have to askctp@fda.hhs.gov. Chrissie?

MS. CAI: Okay. Good morning. My name is Chrissie Cai. I am the data quality management team supervisor here in the Office of Science. So as you can see, I'm a data person so I am going to talk

about data and particularly data standards today.

So before I get started, I like to get a pulse of the audience. How many of you know about data centers? Oh, good. How many of you know about CDISC data standards? Great. Great. Good to see some hands were raised.

Okay. So my presentation today is in two parts. First of all, I am going to talk about CTP data standards. And then I will be getting to the details of this first Tobacco Implementation Guide, which is our first data standards.

So why data standards? You may be wondering why. I think a lot of us are using standards, but we are just not realizing it. For example, like today's presentation, we all follow the same standards. It has the same look and feel, same font, same color, same footer.

This is a way of standardizing our presentation so you can always see the same -- get the same information. The text is on the left-hand size. The picture is on the right-hand side. So that is one way of the standards.

So standards to FDA is also very important, not only FDA but also industry. For decades, FDA has supported and benefitted from the development and use of standards to support the agency's mission in protecting and promoting the public health. Effective and meaningful participation in the standards development organizations for the products FDA regulates are critically important.

The use of standards can increase predictability, streamline premarket review and facilitate market entry and used for safe and effective regulated products.

So what is data standards? Data standards is nothing but just a consistent general framework on how a particular type of data should be structured, defined, formatted or exchanged between computer systems, not between human beings.

And there are standards for everything, from how blood pressure is collected to how regulatory materials are submitted electronically to FDA, but only some standards are required.

As you can see on the right-hand side, FDA has this Data Standards Catalog that is published. Actually, I just got information last week this Data Standards Catalog was just updated last week so you can go to FDA's website and take a look. So far CTP does not have any data standards published in this catalog, but we will soon join this effort.

So now let's talk about CTP's data standards strategy. We have an internal data strategy from 2021 to 2025. It's a five-year plan. So right now we are in the middle of this strategy.

So what it does is it outlines the strategies for the development and dissemination of data standards to better support the programs of CTP through better and more meaningful data.

It also supports CTP's public health mission through predictable, consistent and high-quality data standards. Some areas included are electronic data exchange standards, premarket and post-market review, which I will be talking a little bit about these in the next two slides. And, of course, we focus on quality, policy, planning and

governance.

So first it's the electronic data exchange standards. My colleague will be talking more about these in detail this afternoon. I just want to touch upon a little bit about this.

So we do utilize this technical specification document, which was also recently being updated, and it's on the website. You can take a look and download.

So some of the files that are supported are Excel files and SAS transport files. Please do not convert these files into PDF.

Premarket and post-market review. Lauren talked very in detail about how we use OMB forms for our PMTA review so just to reiterate the importance of using forms for us to collect data. Another example is 4057, 4057a, 4057b, those three forms, that you can use.

All right. I want to touch a little bit on this grant program, the CDISC data standard -- the data standards grant program. This grant program was published about two years ago. It's been going on

very well. And this is a collaborative agreement, which is a support mechanism used when there will be substantial federal scientific or programmatic involvement. In fact, a new grant was just published also recently.

Our strategic goals include support open, consensus-based data center development. We also maintain and promote a well-defined data centers governance function, promote electronic submission of regulatory data using established standards. Last but not least, optimize CTP's regulatory review processtofully leverage data conformed to standards.

So why? What's the benefit that we can all benefit from? So I think there are four or three R's and four E's. The first R is reduce time in finding data.

What does that mean? It means actually for example a friend of mine would like to send me some data. if we all know what a data set means, what each variable in the data set is, no explanation needs to be done from a friend to me because they all follow the same standard. They all have the same

format. So that reduces time in finding data. Likewise from Company A to Company B or from company to regulatory agencies. We can all use it this way.

The second R is reinforced validations through conformance rules. In the CDISC standards, which I will be going into a little bit of detail, you will see there are conformance rules that are part of this TIG Version 1.0.

And also we use data. It's easier. Because all the data is the same, we can use programs to pull data sets together and reuse them again and again. So that's a huge benefit in reducing our review time.

And the four E's, first of all, ensure the same words mean the same thing. In the standard, we have controlled terminology, so we can all speak the same language. And, of course, because of using the standards, we can empower search and automation capabilities.

Last but not least, we enhance transparency in stakeholder engagement.

Now I would just pivot to Tobacco

Information Implementation Guide, Version 1.0, we call it TIG. This is done as part of the CDISC data standards. So CDISC means Clinical Data Interchange Standards Consortium. For those of you who are not familiar with this, this is for your knowledge.

This guide, TIG Version 1.0, supports the CTP data standards strategy, which I mentioned before, through provision of standards and terminologies to facilitate tobacco research, scientific review, harm reduction and information change.

It is a collaborative initiative with CTP, CDISC and industry stakeholders. And also I don't want to read all of these, but it develops a set of standards, collectively referred to as this TIG Version 1.0. And we anticipate this Version 1.0 will be published in the spring of 2024.

So this picture illustrates this TIG is a single and comprehensive implementation guide. It started from how scientific data is being done and data collection and then through data tabulation, which is data submitted to us or between industries

and also how we analyze data.

Underneath, there is the common language, which is controlled terminology and also measure of adherence, which is the conformance rule. And also CDISC provides their CDISC library as part of this guide.

To address this concept of tobacco studies and translate them into CDISC standards for both established CDISC standards, I want to mention what does that mean? Established, that means there are these standards have been developed already. We just build upon those the already established standards.

Of course, there are new CDISC standards to fill the gaps identified by CDISC and industry SMEs. So these are the five main core rules or standards underneath this guide.

So this timeline and TIG team, it consists of 34 members from 5 disciplines in CTP and 37 industry members from 10 different companies. And we all worked together for last more than a year half, almost two years now, to develop this TIG and now

it's October. It's under public review.

It was just announced last Monday, the public review started last Tuesday actually. You can go to CDISC website and find more information. And later I will mention how you can participate in this public review.

So I want to update you a little bit about the progress, so the scope requirements for TIG 1.0 were complete. Key concepts are identified. Development was completed. And internal review actually was done from April this year until last month. We did several conference presentations and more will be done, more education will be done.

So if you go to the TIG 1.0 and public review, on the right-hand side, that's the table of contents you will see. It's a draft version because it hasn't been published yet. So that's the table of contents you will see.

There are also -- this TIG is also very innovative. Some of the innovation highlights are -- this is actually CDISC's first hybrid implementation guide. It is developed in partnership

with CTP. It is a standalone CDISC foundational standard that serves as a comprehensive resource for the collection, tabulation, analysis and exchange of tobacco product data for submissions to CTP.

It is built upon these models. As I mentioned, those are already defined by other agencies and other organizations. So we just build upon those models, CDASH Model Version 1.2, SDTM Version 2.1, ADaM, so on and so forth.

The philosophy behind the development was really data first and users who use these data and then standards for users who use this data in this order. So data is the key.

We also ensure the instruction is very simplified and concise and organized from highest level concept to detailed concepts. It adhered to the scope of implementation of standards only. It also limits content best describing other resources.

So therefore, use cases that were developed in this TIG against draft, the first one is product description, then there's non-clinical and product impact on individual health and product

impact on population health.

Here is an example of what a CDISC or TIG data set looks like. Sometimes we call it data domain. So this TO as you can see is a table. It's not the wide sort of table. It's a long. So each row has product characteristics. And you can put your product and -- product in one data set. And the one data set can consist of many different products.

Here is another example of an in vitro study. It's a non-clinical in vitro study where it defines how this bacterial reverse mutation asset or test, the data can be formatted in this way.

The data science innovation, this TIG has the CDISC library. It's an end-to-end standards for tobacco studies. The inclusion of informative content and so on and so forth. A lot of the things are very innovative in this development.

So how can you be involved? I want to emphasize on anyone who would like to participate can participate, literally anyone, anyone who sits here. If you would like to be a volunteer, you can go ahead and sign up. There is more information on CDISC's

website about this public review and there will be a webinar on the public review.

So you can sign up for that. We encourage you to volunteer. And if you have more questions, feel free to ask. That concludes my presentation for today.

CDR RUSSELL: It's lunchtime, you guys. We do have lunch options available in the lobby. I think some of you guys have already pre-purchased so you will be able to get your food items. Please keep in mind those lunch options are very, very limited.

And with that, we will break until approximately 1:05. And we will convene at 1:05 and start our second portion of today. Happy lunchtime.

(Whereupon, the above-entitled matter went off the record at 11:42 a.m. and resumed at 1:05 p.m.)

CDR RUSSELL: If everyone could please take your seats so we can begin to get started. So it is approximately 1:05, and we will start after lunch. Welcome back, everyone, to all of you guys who are face to face with us and everyone virtually.

For those of you who are just joining, my name is Commander Avena Russell, and I will be your moderator for the remainder of this meeting. We will continue Section 2 of the required content and format of PMTA submissions. The second group of presenters will be as follows: Deborah Sholtes who will discuss the electronic submissions followed by Sheryl Wood and Fran Weiss discussing FDA Form 4057B, validation tool for PMTA submissions. Welcome, Deborah.

MS. SHOLTES: Welcome back from lunch. I'm Deborah Sholtes, Branch Chief with the Division of Regulatory Science Informatics in the Office of Science. And today I'm going to speak on electronic submissions, some lessons learned, and some common errors that we have seen over the past 13 years.

So I'm going to highlight a couple of things that are new since our last public meeting in 2019. I'll highlight some lessons learned and common errors. I'm going to go over submission organization module by module, talk about the eSubmitter tool, CTP portal, and also make sure you have plenty of references for getting help.

So since the last public meeting in 2019, what's new with rules is that SE and PMTA rules are final. And the language in both is pretty similar. The meaning is the same.

All required information needs to be provided in electronic format that FDA can process, review, and archive. The key word there is must. So before you get started on your submission, I recommend that you find, locate, highlight, favorite, print the electronic submission file format and specifications document.

This is a document that is periodically updated and actually was updated as recently as two weeks ago. So we're up to Revision 6. This is the link.

So the good news is that most submissions come in and are processed without issue. And the characteristics of a successful submission are that the eSubmitter package is complete. The file path and name do not exceed 200 characters with spaces.

Now someone in this room who is familiar with the file formats is looking at me and saying,

200? I thought it was 180. Well, that's one of the new things that was just published two weeks ago is that the file path has been extended from 200 characters with spaces -- I'm sorry, from 180 to 200 characters with spaces.

So a successful submission will include files that reference the submission module. It will use short descriptive file names and file paths. As an example, 1.0mainTOC.pdf or something like 4.2study1.xpt for a SAS transport file.

A successful submission will have links from an index to files that are active and work. And you can test this by putting your submission into a new location from other than where you created it and checking each of the file links to make sure that the documents are present and that they open. And you can also track file count to ensure that all files are packaged.

So if you know that you have 200 files, you want to be able to track that through the submission process. So successful submissions will include analysis data sets that are in SAS transport

files or .csv files. FDA forms that are Excel will be submitted as .xlsx or .xls and not as .pdf.

PDF files will be created directly from a document source. So if you write a summary document in Word, you'll save it as .pdf from Microsoft Word. You'll be consistent with the company name, address, and email, and it'll be the correct legal name on the FDA forms and documents that is the same company name used to create the CTP portal account.

So about half of the submissions that have issues with processing have issues with the eSubmitter packages. So characteristics of submissions that FDA cannot process are when the eSubmitter packages are opened after they had been packaged by eSubmitter. And when that happens, eSubmitter -- actually the act of opening those zipped files will create a zero sized file which then gets sent along to FDA, and FDA security recognizes that as a risk.

And it will either stop or delay processing. So you don't want to open those eSubmitter packaged files. Also, we cannot process

files that have password protection.

We can't process files that have forms with foreign characters. We can't process files that have file names and paths that exceed 200 characters with spaces. And we have issues when the company name or address are listed differently from the portal account.

So some common errors -- some common eSubmitter errors are creating a submission using the wrong submission type. We see this most with master file submissions where PMTA is selected instead of master file. A master file may be used for PMTA review.

However, we have a submission type for master file. Not checking the document links before packaging sometimes results in missing documents. So you may intend to send 200 files but actually only 198 were packaged.

So you need to make sure that you know how many files you want to send and make sure that number is consistent through the process. Another common error is variations in the company name. And

that can be any kind of variation. A company name has the legal company name and then the company name that perhaps you're used to using in common conversation.

And that will be a problem for the computers that are looking for the legal company name. With large submissions, we sometimes see that the packaging of the modules is done independently. So while it's a good thing to organize the submission by module, you should let eSubmitter do the packaging of all of the modules.

So separately packaging modules 1 through 7 in eSubmitter means that you're going to have seven separate uploads. And the system will create seven separate submission tracking numbers. And not only is it a challenge then to associate all of the submissions correctly but any hyperlinks that existed anywhere between those seven will be broken.

Another issue with large submissions, this is more frequently where we see the file paths that are too long. And sometimes we also see deep into the nested folder structures that one file that

has a password protection. So this is an example even with 200 allowable characters with spaces, the .xlsx -- it's hard to say -- means that the entire file path is going to throw an error.

Okay. So these are some positive things that you can do to make your submission more readable. So a structured submission breaks the submission into logical discrete sections. It separates content by discipline.

It helps you know what to call things and where to put things. And it helps reviewers know where to find things. So CTP has learned from other FDA centers to organize a submission by different types of scientific material.

And this model is based on the five module concept, the model from the electronic common technical document. We've added two additional modules, module 6 and module 7. So the first module is the administrative section.

And here's a tip. You can use these table of contents numbers in your file name, and that will help make your files findable. So if a reviewer is

looking for a particular section, they might use the module number as a search term.

So in the administrative section, that would include the cover letter. And so your file name might be something like 1.2coverletter.pdf. That 1.2 will make it easy to find.

Module 2 includes the summaries. Module 3 includes product description and manufacturing, and this includes ingredients. Module 4 includes nonclinical information.

Module 5 is the clinical product impact on individual health. And this is where we somewhat deviate from the rest of FDA. We've added module 6, clinical product impact on population health, and module 7, environmental impact.

And if you refer to the file format and technical specification document, you'll find that detailed in Appendix A. So I'm going to go on to the eSubmitter tool. So this is the link to the eSubmitter tool.

The eSubmitter tool is old technology. It's not a web-based application. It is something

that has to be downloaded to your desktop. So best practice is to check for the latest version and review the documentation for the eSubmitter tool.

This is what you're going to use to create the packages to upload via CTP portal. So after you've checked for updates and open it, you're going to create a new submission. You're going to select a CTP template, and then the template will step you through preparing the submission documents.

When you're done, when you've attached all of the files that you intend to attach, so all 200 files if that's what you're going to send, you'll select package. And there's a little icon that looks like a package. And you tell it to package and it does. It creates ZIP files.

And it might create one ZIP file if you have a reasonably small submission. Or it might create six or eight or ten or whatever number of packages it needs to in order to create packages that CTP portal can upload. And eSubmitter and CTP portal are aligned with each other.

So eSubmitter knows what CTP portal can

upload. Oh, and what should you not do with those packages? Should not open them. Save them locally so that you can upload them to portal, but trust eSubmitter. Don't open the packages.

So here's some additional resources for eSubmitter. There is quite a lot of material on the website. It says CTP portal. CTP portal is what we use to upload those eSubmitter packages.

And you can also use it to view administrative information regarding your submission. And this is the link, and this is what the login page looks like. The welcome screen gives you a summary of the most recent uploads and the most recent files.

This is what the upload tool looks like. This is where you go to start uploading your eSubmitter packages and where you can view your prior uploads. So how do you get an account?

First, you have to request an industry account, manager account. The IAM is the person who will create user accounts for your company. FDA will create one IAM account for an organization, and then that IAM can create other user accounts to suit the

needs of the company.

So the IAM that we will create an account for, that request will be created by an authorized representative. So it's not anyone who can create an IAM account. You have to be an authorized representative.

And part of that process after you've completed the form, you will receive as an IAM an email to complete the process. The link in that form is active for 24 hours. And each of the portal accounts that are created will need to be reset every 90 days.

Those are FDA security protocol. They're not negotiable. So this is the link to the web-based form. The IAM also has to read and acknowledge each of the rules of behavior.

And a difference from CPT portal in 2016 when we first rolled it out was we would allow in 2016 IAMs to not be authorized representatives of the company. But we no longer do that. And so you must be an authorized representative for us to create your account.

So the authorized representative who's a direct employee of the organization is the one who completes the form. They will include the full legal name of the organization as spelled for DUNS. Do not use acronyms. Do not write self-employed.

Do include the full legal address of the organization. Do not include a personal address. Do include the correct email address for the organization.

And ensure signatures are on both of the forms. The authorized representative signs the IAM form. And the individual that they designate that can be either the person -- the authorized representative or someone who they designate. They have to sign the rules of behavior.

So companies are responsible for managing their accounts, and they are responsible for the behavior of their employees and their agents. So if they delegate authority to an organization such as a lawyer or a consultant, the company is still responsible for the behavior on CTP portal of the agent and are responsible for managing their portal

accounts. So that includes things like ensuring that they are refreshed every 90 days and that portal accounts are deleted when someone leaves the company.

So one company should have one portal account. One portal account will show the uploads submitted for that particular account. If somehow a company has created more than one account, and it has happened.

You will only see in each account those uploads that were uploaded under each one of those accounts which means that no one in the company can see all of their uploads. So if that has happened, you want to contact CTP so they can consolidate those accounts. There are lots of resources on the website.

The eSubmission's help desk knows how all of these things operate. And they can either answer your questions or direct you to other resources that can help you. Lots and lots of material on the website. And if you have questions, you can ask during the panel. Thank you.

MS. WOOD: Hi, I'm Sheryl Wood. Fran Weiss and I will be presenting about the enhanced

4057b product grouping -- PMTA product grouping spreadsheet and the validation tool. So while we're the ones presenting this information, it represents collaborative work here at CTP and the work of many staff.

We are optimistic that these enhancements will improve your knowledge and experience completing the 4057b form. And it will also increase the number of submissions that CTP is able to move through acceptance and filing. We'll be covering the enhanced FDA 4057b form instructions, where to find the 4057b instructions and tools, a summary of the instructions, how to avoid common issues completing the form, and the new Validator Tool.

So the enhancements to the 4057b instructions across three different documents and tools. First, we updated the electronic submissions file formats and specifications document with a new Appendix B. The appendix provides guidelines and instructions for completing the 4057b product grouping spreadsheet.

We also have enhanced the FDA 4057b PMTA

product grouping spreadsheet. We have added an instructions tab. We've automated the spreadsheet to avoid common errors.

We've added hover-over instructions on column headings. And we've added error messages. And last but not least, we developed a 4057b Validator Tool that can be used to verify that the product grouping spreadsheet has been completed correctly.

So all of these enhanced products can be found on the FDA website. And there are links provided here to the exact pages. So now I'll review the product grouping spreadsheet.

Once you navigate to the site, you can download the form. Notice there are two tabs that appear when you first open the spreadsheet, an instructions tab and an introduction tab. It will open to the introduction tab.

So first, you'll enter applicant name. The name required here is the name utilized to register for your industry account manager or IAM account. And this appears on your application cover letter.

Best practice is to use the name listed in Dun & Bradstreet. Next, select the product category and subcategory using a drop-down list. The application type is pre-filled since 4057b is only used for the PMTA application.

Next, click on the enter unique product properties button. Once you select enter unique product properties, the spreadsheet opens to a third tab called products. Notice that the form is designed to display only the product properties associated with the product category.

And this is as noted in the PMTA rule. Some columns are hidden. Do not unhide columns and enter data into those fields. This will cause the 4057b form to fail when it's submitted.

There's also a table in the PMTA rule. And 21 CFR 1114.7(c) of what properties are required based on product category. On the product tab, enter one product per row.

If you encounter an error or want to see instructions, you can navigate to the instructions tab. Here you will see all of the column headings

for all of the columns left to right. So the columns work left to right in the same order as they appear on the products tab.

So it starts with product name, TP number, package type, et cetera. On the product tab, you can also hover over the column heading and the instructions will appear. The hover only instructions are only viewable on the column heading, and these are the same instructions that are on the instructions tab.

So you have two ways to get to your instructions. Now I'll provide a summary of the instructions for completing the spreadsheet. I'll then show some examples of some real common errors that we have found on submissions and how to avoid them.

So first, do not edit the spreadsheet in any way. Unhiding columns will cause the submission to fail. Enter only one product category and subcategory per spreadsheet.

You'll need to prepare a separate spreadsheet for each product category and

subcategory. Use the enter unique product properties button on the instructions tab to see the columns allowed for your product category and subcategory. Lastly, use the reset button to clear fields if the spreadsheet is then going to be used for a different product category or subcategory.

Use the hover-over instructions or the instruction tab for guidance on what is acceptable in each column. I just showed you these. Use the drop-down lists to ensure you're selecting allowable entries. I'll show you the drop-downs in a minute.

Even if you're copying and pasting data into the spreadsheet, make sure to check the drop-down lists for the correct values allowed for that column. If you do not have an entry for a field, leave it blank. Do not enter none, n/a, or a slash.

Use English characters -- use only English characters. Special characters cannot be processed such as an accent or an n/a. We have seen these flavors such as creme brulee and pina colada.

We'll explain in a latter slide where certain special characters are allowed and in

specific columns. Next, look for dependent columns to ensure they're complete. For example, if you enter a numeric value, you must enter the unit.

For example, if you enter nicotine concentration, you must select a value such as mg/ml. Limit the spreadsheet to 5,000 products. Divide products across additional spreadsheets if necessary. Save and submit your file as .xls or .xlsx, not a PDF.

So here's some common issues that we've encountered processing spreadsheets that have been submitted. Only one product category combination is allowed per spreadsheet. We've automated the spreadsheet to prevent this error.

Illustrated on the left where both open e-cigarette and open e-liquid are selected. On the updated spreadsheet, the additional set of rows only appear if other is entered for the product category and subcategory. When other is selected, you'll need to provide an explanation and the additional rows that appear.

We see a lot of errors in the TP number

column. Tobacco product number is a number assigned when a product is registered in TRLM-NG. The number is formatted with a TP at the beginning.

It can be up to ten characters in length including that TP. This is an optional field. But if you have the TP number for a product, we encourage you to enter it here.

If you don't have it, please leave this field blank. This number is not a product ID that your company may use or SKU number. Use the drop-down list to make sure you're using allowable entries.

Note that there may be differences for entries of similar fields. Example here shows the package type is bottle with no S. And the units product quantity is bottles with an S.

Also note the allowable units for fields. An example here shows that nicotine concentrations are mg/ml, %W/W, and mg unit. If you select mg unit, you need to specify the unit in the next column.

Characterizing flavor is another place where we encounter issues. So first, you select the characterizing flavor from the drop-down list. There

are four options: menthol, tobacco, flavored, and unflavored.

If you select menthol, tobacco, or unflavored, leave column L characterizing flavor if flavored blank. Only when you select flavored in column K characterizing flavor, you'll then need to enter description of the flavor in column L, characterizing flavor if flavored. On the screen with the green checkmark, you see that only the row with flavor selected has a description of the flavor as peach mango.

The examples with red axis show errors when someone selected tobacco, menthol, or unflavored and did not leave the next column blank. In the left example, someone selected menthol and tobacco and then repeated the entries in the next column. That next column should've been left blank.

The middle example shows someone entered unflavored and then none in the next column. The none entry is not needed and should be blank. The right example is also an issue.

It has flavored selected, and then

tobacco in the next column. If the characterizing flavor matches one of the three selections of tobacco, menthol, or unflavored, that should be the selection in the first column with the second column blank. This is a required field for all product categories and subcategories.

If the product is a component such as a battery or a coil, select unflavored. For any of the drop-down lists that include a selection of other, please fill in a description of what other means. If you enter other and leave the other column blank, it will cause errors.

Shown here is a package type of other with nothing entered for the package type if other. Just a note with this example of other, there's a real case where there was no package type and the e-cigarette was sold as a single e-cigarette with nothing containing it. By stating e-cigarette as another package type, the form will not error for this field, and it's an accurate statement of the package type.

Similarly, if you enter a numeric value,

you need to enter the unit for the numeric value and vice versa. We have encountered units with no numeric and numerics with no units. These columns are always next to each other. Shown here is length, numeric value, and units length.

In the open text fields for product name and characterizing flavor if flavored, use only English characters. This is the list of the allowable special characters for these two columns. This means if you enter flavors again like creme brulee or pina colada, you'll have to do it without the accent or the ene.

Using special characters outside of those listed here or in other places besides these two columns will cause processing errors. The copy and paste functions are still available. We know this is important functionality, especially when entering similar products.

But if you use copy and paste in the spreadsheet, the error messages will not work. So if you use copy and paste, be extra careful to ensure that you're using allowable values and correct values

from the drop-down lists. If you do use copy and paste, we've created a Validator Tool that you can use to verify that your entries are correct. So now I'll pass the presentation to Fran Weiss.

MS. WEISS: Thanks, Sheryl. Good afternoon, everybody. This last portion will be about the FDA 4057b form Validator Tool. I don't know which button to use. I guess that button. Sorry.

The use of the Validator Tool is completely voluntary. But it does have many benefits. The tool is found on the FDA website and we provide the link right here.

If you use the tool, you will minimize the chance of processing errors and reduce time spent reviewing, correcting, and resubmitting the form. It also ensures that we at CTP will be able to load the products into our system and without issues that slow down the process. The system requirements are noted here, and the Validator Tool is 508 compliant.

The Validator Tool will run in Windows. You will download the application onto your computer and run it. This way, the product data stays on your

computer and is not going out to the cloud or any outside system.

This is the main screen for the Validator Tool. It's an interactive screen and it has three steps. One, you choose your file. Two, you validate the file. And three, you either download a certificate of completion or you download an issue spreadsheet which will assist you in correcting any errors.

So when you click on choose file, you'll have a popup for you go select the Excel spreadsheet that you need. Remember we only accept .xls or .xlsx. Under step one, now you can see the file name that you selected, and you just simply press the validate button.

Once the form process and in this case is successful, you will receive a message. And the button displays for you to download the completion certificate. When you press the certificate -- completion certificate button, a popup will appear for you to save the document, and you can navigate to where you want to save it on your system.

This is our happy path. This certificate can be submitted with the application, but it's not required. It contains the company name, date, time of validation, and the file name.

It also includes the product category, subcategory, and the number of products that were processed on the spreadsheet. Please note successful validation does not mean your application contains all elements required for acceptance of your application per 21 CFR 1105.10 and 1114.5. Now we're going to choose a different spreadsheet so we can show you an example of a failure.

We've chosen the file and we're going to select the validate button. In this case, the validation has failed. Instead of having a button for the completion certificate, you have an issue report which is also downloadable just like the certificate.

You'll be prompted to save it. Okay. So this is going to look very much like the 4057b validator spreadsheet -- I'm sorry, the 4057b spreadsheet. Rows without any errors are going to be

hidden. So you'll only see the rows that have issues.

The error messages are found by scrolling way, way, way over to the right. Displayed is the original data row number of the product, a status, and the error message. The message appears in this specific product row.

These messages are provided so that you can correct the original spreadsheet, then you can re-validate the spreadsheet to ensure everything has been corrected prior to submitting to CTP. We're going to take a look at just a couple of the error messages. Units, product quantity, Column F, if product quantity numeric value is set, then units product quantity must have an entry.

If you do not have values for a field, you must leave the cell blank. Please refer to the pre-market tobacco product applications and recordkeeping requirements rule for the required properties based on product category and subcategory. These two columns are dependent on each other.

If you enter a numeric value, you must enter a unit and vice versa. With respect to leaving

the cell blank, this refers to both columns as a whole meaning if you don't have a numeric value and a unit, leave them both blank. Please do not enter any form of n/a or none.

As you can see in this first row, the highlighted area, we have a product quantity but no units. In this cell, to correct this area, you will need to enter the missing units in the original spreadsheet and then re-validate. Characterizing flavor, characterizing flavor if flavored, Column L, if you select tobacco, menthol, or unflavored in characterizing flavor, please leave characterizing flavor if flavored blank.

If the product is flavored, then characterizing flavor must equal flavored and characterizing flavor if flavored must be populated. That's a lot to say. But basically, there's four things you can chose: menthol, tobacco, flavored, or unflavored.

If you enter flavored in Column K, you must enter what the flavor is in Column L. If not, if you enter anything else, please leave

characterizing flavor if flavored, Column L blank. Therefore, in this example, we have menthol as the characterizing flavor and extreme sweet mint as characterizing flavor.

The way to fix this is just to remove extreme sweet mint from Column L. We sincerely hope these enhancements to the electronic submission file format and specifications, the 4057b PMTA product grouping spreadsheet, and the Validator Tool will support your process to develop the submissions that contain correct and accurate product properties by category, subcategory. Sheryl and I thank you very much.

(Applause.)

CDR RUSSELL: Thank you all for your presentation. I know we have all probably experienced some challenges with the 4057b. We will now go into our next session, Section 3, who will be presented by Kris VanAmburg providing us with an overview of substantial equivalence reports and a new proposal for triage. Welcome, Kris.

MR. VANAMBURG: Good afternoon. Thank

you for joining us today for today's discussion on updates on substantial equivalent reports or SE reports. I'm Kristopher VanAmburg, Supervisor Regulatory Health Project Manager in the Division of Regulatory Project Management in the Office of Science for the Center of Tobacco Products.

Our discussion agenda includes overview of substantial equivalence, the SE review process, our current SE status, SEQ and prioritization, and helpful tips. First, a brief overview of substantial equivalence or SE reports. SE reports are an alternate pathway for authorization of a new tobacco product.

Under Section 905(j) of the FD&C Act, an SE report can be submitted by any manufacturer for any new tobacco product seeking an FDA marketing order. Before a new tobacco product can be legally marketed using this pathway, an SE report must be submitted and reviewed by the RDA to determine substantial equivalent to an eligible predicate product and in compliance with the requirements of the Act as defined in Section 910(a)(2)(a) of the

FD&C Act. The statutory authority for SE program can be found in the Tobacco Control Act.

It provides the framework and the standards for the SE program. The refuse to accept rule which was published December 29th, 2016 and effective for all SE reports received after January 30th, 2017 describes when FDA will refuse to accept a tobacco product submission or application because the application has not met a minimum threshold for acceptability for FDA review. Examples for a refuse to accept are SE reports that are not in English, SE reports that do not pertain to a tobacco product, or SE reports that do not identify the type of submission.

This rule allows FDA to focus the review, resources, and submissions that meet a threshold of acceptability and encourages quality submissions. The SE rule was published on October 5th, 2021 and effective for all SE reports received on or after November 4th, 2021. This provides additional information on the content and format of the reports intended to demonstrate the substantial equivalent of

tobacco product and SE reports.

The rule also establishes the general procedures FDA intends to follow when evaluating SE reports, including procedures that address communications with the applicant and the confidentiality of the application. Similar to PMTAs, there's an opportunity for pre-submission meetings. When considering the timing of a submission, applicant should review our meeting guidance and ensure that enough time is available to incorporate the advice provided during the pre-submission meeting.

Now let's quickly move through the SE review process. You will see some similarities to the PMTA process described earlier in the presentations. As with PMTA, SE reports also have an acceptance phase which will result in a decision of the application either being accepted or receiving or refuse to accept letter.

This slide is a short summary of acceptance requirements over time. As you can see, the criteria for acceptance has increased over time

with regulations. Of importance is the SE rule which impacts applications received November 4th, 2021 and later.

This rule requires the use of FDA forms, the date the SE report was submitted, previously assigned or relevant system tracking numbers or STNs, name and contact information for the authorized representative or the U.S. agent, unique identification of the new and predicate tobacco product, address, and FEI numbers of the establishments involved in the manufacturing or importation of the new and predicate products, description of the new and single predicate tobacco product, identification if the new tobacco product has the same or different characteristics from the predicate product, additional environmental considerations, and signed certification statements. The purpose of phase one acceptance is to determine if the new tobacco product falls under CTP jurisdiction and certain basic regulatory requirements are met.

Phase one concludes with the issuance of

an acceptance letter or a refuse to accept letter. Issuance of an acceptance letter moves the SE reports to phase two. Issuance of a refuse to accept letter completes the review process and the applicant has the option of reviewing the deficiencies and the refuse to accept letter in submitting a new SE report.

When an SE report is accepted, phase two starts with the review of the predicate product to determine if it qualifies as preexisting status and is predicate eligible. If the predicate is found predicate eligible, the SE report will move to scientific review. However, if the name predicate product is not predicate eligible, FDA will move the SE report into phase three, scientific review and action, and issue a not substantially equivalent letter.

We will now move to phase three, review. The purpose of the review phase is to conduct a scientific assessment to determine if the new product is substantially equivalent with respect to the predicate product. Generally, SE reports are assigned a chemistry, toxicology, engineering, and

environmental reviewer.

Additional scientific evaluation may be needed as decided by the technical project lead. For example, additional reviewers can include social science, behavioral clinical pharmacology, and microbiology. Upon completion of review, we will decide if the application contains enough information to make a final determination.

If enough information is not provided, FDA will issue a deficiency letter. If enough information is provided, we will determine whether the new tobacco product is substantially equivalent, SE, or not substantially equivalent, NSE, to the predicate product. After completion of review, the application will enter the action part of phase three.

If the application is found scientifically SE, FDA will then address the environmental considerations. To grant marketing orders, FDA must prepare an environmental impact statement or a finding of no significant impact. If the application does not contain sufficient information, we will issue an environmental

information request letter.

Once the environmental considerations are satisfied, FDA will issue the SE order letter and contact the applicant to offer a courtesy copy. The final technical project lead review and the order letter will be posted to the FDA website. If the application is found not substantially equivalent, FDA will end the review process, issue the NSE order letter, and contact the applicant to offer a courtesy copy via email.

For applications that have been marketed prior to the NSE decision, the final technical project review and order letter are posted at the FDA website. For those products, FDA offers courtesy copies of the NSE letter, the technical project lead review, and the last cycle of scientific reviews that support the NSE decision. Applicants can submit amendments to SE reports at any time prior to a final decision.

Amendments may not be reviewed by the FDA until the next cycle. Amendments can be submitted for redaction requirements if a health information summary was provided. Please note amendments for SE

reports received November 4th, 2021 and later require FDA Form 3965.

This form is titled The Tobacco Substantial Equivalence Report Amendment and General Correspondence Submission Form. We will now discuss the current status of SE reports with the FDA. As of the end of fiscal year 2023, September 30th, 2023, FDA has received a total of 15,775 SE reports.

Of the more than 15,000 applications received, CTP has completed phase one and issued decisions on approximately 94 percent of the applications with 12,470 acceptance decisions and 2,357 refuse to accept decisions. Unlike PMTA, there is no filing stage. The notification stage will result in a finding that impacts the decision in phase 3.

In phase 3, CTP has issued 1,842 substantial equivalent orders and 502 not substantial equivalent orders. As you can see, a number of SE actions are authorizations for legal marketed products. FDA has closed approximately 59 percent of all SE reports received.

There is still a significant percentage of SE reports that require a decision. Understanding the number of pending SE reports and the fact that prioritization has not changed since the receipt of our deeming bolus, we will now transition to what is on the horizon. We will now look at the SEQ and the FDA prioritization of SE reports.

In response to the regulation asserting jurisdiction over additional tobacco product categories, also known as the deeming rule, FDA received approximately 6,800 SE reports from 105 different applicants. Due to the large number of applications, FDA developed a process to determine the review order for all applications. This process applied to all applications that were submitted to CTP by September 9th, 2020, including originally regulated products such as cigarettes and smokeless tobacco and deemed products such as cigars and water pipes.

For SE reports, a review order was determined by using a -- by randomization by manufacturer. Regardless of the tobacco product

category, using a basic random number generator, FDA assigned a number to each applicant that submitted at least one application. This number determined the order for that applicant's products to enter the acceptance review and subsequent review phases like notification and substantive review.

At the substantive review phase, if the number of products submitted by the applicant exceeded the capacity of the scientific review team which was set at 20 products per team, FDA assigned a second random generated number to each product and each submission to determine the order of the products. The products that are not assigned to the review team would remain in the queue until all the manufacturers with timely accepted applications have had the products enter the substantive review phase at least once. This ensures that every manufacturer has an opportunity for some of its products to enter substantive review.

The randomly generated numbers stay with the application for the individual product and continue to determine its place in the queue

throughout the review process. While this was a way to create fairness regardless of the manufacturer's size of number of products submitted, we are currently considering a new approach to address new concerns and prioritization. To ensure that our practices continue to meet current needs, FDA reevaluated past prioritization strategy, review practices, and considered stakeholder feedback.

From this assessment, FDA determined that a new approach will better address the needs of the program. While the initial purpose of the prioritization strategy was to level the field for all applicants, regardless of size or the number of products submitted, new areas of focus have been identified. For example, there's a lack of predictability for when an application would be received would be reviewed.

As FDA had 105 manufacturers with at least one SE application, not all applications could be kicked off at the same time. FDA has not made a public list available with the review order or current status for each applicant. Due to this, manufacturers

could not prepare for their turn in the queue.

Furthermore, when an applicant was next in line for a review, they received a heads-up notification for the first cycle of products. However, the manufacturer was not provided any choice in what product would be reviewed as it was determined through randomization. This was problematic for several reasons.

There may be multiple product categories. As one product category is reviewed in a cycle, the first category to display a randomization was selected. This may or may not be the category that an applicant would want to prioritize for review.

With randomization, review efficiency was lost for products with similar modifications. As randomization order was followed, FDA did not always place the same modifications into the review bundle. This resulted in similar modifications, receiving a few review and different review cycles instead of within a single review cycle. And last, as discussed on the previous slide, this was a static list.

As such, any SE reports submitted after

September 9th, 2020 were not included in the queue or randomization. These later applications may be of more importance to review for either industry or the FDA. Due to the growing number of pending applications and concerns about the lack of prioritization have been raised, FDA is considering a new approach for prioritization that may be more inclusive of all pending applications.

Based on our evaluation of past practices, understanding the limitations of a static prioritization strategy, and identification of new areas of focus, FDA is proposing to allow manufacturers to select which of their pending applications should enter scientific review and where possible applications with similar modifications will be bundled together. The goal is to increase the applicant's involvement in the prioritization process and create opportunities for review efficiencies. FDA is also considering the use of a dynamic priority list instead of a status priority list.

FDA is considering how computer-based randomization can be used to fairly determine review

order for all current and future applicants. The goal would be to ensure all current and future applicants are included in the scientific review queue. With these two potential changes, we aim to make the prioritization process more transparent and more predictable.

So let's discuss how this process would work. The dynamic priority list would include every applicant who has a pending application. If an applicant is not currently listed, upon receipt of their application, they would be added to the dynamic list.

Additionally as previously mentioned, applicants would be provided an opportunity prior to review kickoff to identify the priority order of products for review. Although applicants would be provided this opportunity, FDA would review the final list and ensure that similar modifications are placed together and increase efficiencies. And last, FDA aims to increase transparency of the review process by providing applicants their position on the list, the frequency of kickoffs, and the staff of where FDA

is with the review.

To clarify how a dynamic list process could work, let's start by adding an applicant to the list. First, every applicant that has an SE application pending would be listed on the dynamic list. FDA is considering how computer-based randomization can be used fairly to determine the review order for all current and future applicants.

These applicants would be randomized and placed in order based off the random number. So for example, there are three applicants with pending SE applications. Applicant A has one pending application. Applicant B has 50 pending applications. And Applicant C has 200 pending applications.

They're all assigned a randomized number. Those randomized numbers are then placed in order to create a list. This list would be made available to ensure applicants know where they fall on the list.

As you can see, this list only provides the applicant's name and not how many SE applications are pending. If an applicant is not currently on the

list upon receipt of the new SE application, the applicant would be added to the bottom of the list in the order received. When multiple SE applications are received by different manufacturers on the same day, the order would be determined based on the receipt date and time meaning the applicant that is received by CTP's document control center earliest would be listed prior to new applications received later in the day.

As this list would have new applicants added, FDA will provide updates as necessary. To increase applicant involvement, FDA is proposing to issue a notification letter prior to scientific review that would allow 30 days for the applicant to prioritize products to enter the SE scientific review process. Applicants would be provided criteria and a letter for product selection.

We will discuss the criteria on the next slide. FDA would review the applicant's response to verify the proposal meets the criteria. And if no response is received, FDA would determine the review order.

Again, if no response is provided, FDA would select the applications for review on the applicant's behalf. In general, the proposed criteria which would be provided in a letter would include products with the same category. The product categories FDA currently recognizes are cigarettes, roll your own tobacco products, smokeless tobacco products, electronic nicotine delivery systems, cigars, pipe tobacco products, water pipe tobacco products, heated tobacco products, and a category of other.

So for example, if an applicant submitted SE applications for cigars, pipes, and smokeless, only one of those categories such as cigars would be selected and the other two categories would wait for another review cycle. Products under the same manufacturer, we do understand that there are some overarching groups that submit SE applications for multiple subsidiary companies within their umbrella. We also understand that there may be an agreement between manufacturers.

But this will help ensure fairness.

Products for which applicants have been accepted, if an SE application is pending or received, it would not be included within what is available to prioritize. This is to ensure that an application that may later receive a refuse to accept letter is not pulled into the review queue.

Products with the same or similar modifications should be grouped together to be reviewed in the same cycle. This would increase the efficient and consistent decision making process for similar modifications. In general, a maximum of 25 products will enter scientific review for an applicant.

As each SE application is a one-on-one comparison between a new and predicate product and requires predicate eligibility review, characteristic comparison, and analysis. This is the number we have said is the maximum amount for each review team to ensure predictability in completing the SE review efficiently. Understanding that other factors may play a role if a manufacturer prioritizes all pending accepted products, FDA can more fully understand the

priorities for each applicant.

Now that you have a sense of the criteria, let's highlight some additional considerations. On November 4th, 2021, the SE rule went into effect. For SE applications received prior to November 4th, 2021, predicate eligibility and scientific comparison occurred at the same time.

Post-rule SE applications, those received November 4th, 2021 and later, will move through predicate eligibility prior to scientific review. This means that for those SE reports that are post-rule applications, once an application is accepted, the predicate is set. If an applicant wishes to change the predicate, a new application is required.

For post-rule SE applications, if the applicant does not provide adequate evidence to support predicate eligibility, scientific review will not commence and the product will be found not substantially equivalent. Additionally for post-rule SE applications, if an applicant does not respond to a deficiency letter within the requested time frame, the product will be found not substantially

equivalent or NSE. In general, FDA does not intend to grant extensions of time to respond.

FDA would like to offer some helpful tips and reminders. Remember to utilize FDA Forms 3964 and 3965 for all new applications. As a reminder, if an SE report was received after November 4th, 2021 and does not contain the required forms, it will receive a refuse to accept letter.

And if an amendment does not contain the STNs of the original application, it will not be linked. And as such, it will not be considered or reviewed. Review your application and ensure it contains all information needed to support a substantially equivalent finding, including ensuring all documents to support predicate eligibility is included and verifying that you have the right to reference and utilize a tobacco product master file. A pre-submission meeting may be helpful and may address questions to create a stronger application.

FDA is committed to addressing the SE backlog, improving transparency, and increasing efficiency. These next two slides provide some

helpful resources. Our web page contains a nice overview of the SE process and allows you to view FDA SE findings.

Additionally, we encourage you to become familiar with the various rules and guidance which are listed on the next slide. The decision summaries may be also a useful tool as you prepare future SE applications or respond to deficiency letters. These are the guidance documents that you may find helpful that we referred to on the previous slide. These are for your reference.

Please save any question for the panel discussion. And alternately, you can submit questions to askCTP@fda.hhs.gov. Thank you for your interest and attention while discussing updates on substantial equivalent or SE reports.

(Applause.)

CDR RUSSELL: Thank you, Kris. We will take a short break. We'll reconvene approximately 2:30, and then we will go to our panel session for this meeting.

(Whereupon, the above-entitled matter

went off the record at 2:14 p.m. and resumed at 2:31 p.m.)

CDR RUSSELL: If everyone could have their seats, let's welcome back. It is approximately 2:31, so I gave you all one extra minute today. And this now brings us to the panel session for our question-and-answer period of this meeting today.

This panel will discuss questions from Session 1, 2, and 3 only. As mentioned earlier, we are taking live questions from our virtual and face-to-face participants. There are microphones located in the center of the aisle for those of you who would like to ask a question of the panelists.

I have some questions from our virtual audience, and we will begin. We have four FDA panelists here from the Office of Science, and they will be present to ask your questions. Let's extend a warm welcome to first Ms. Cristi Stark.

Cristi serves as the director of the Office of Science, Division of Regulatory Project Management. She has over 20 years of experience at FDA, including 13 years as CTP. Within her time at

CTP, she had served in multiple areas in the areas of project management, designated federal officer, and policy.

In these positions, she has aided with the proposal development and implementation of rules, guidance, policies and procedures around the handling of review submissions. In her role, she is responsible for the oversight of regulatory processes and review procedures associated with submissions handled within OS. Prior to working at CTP, Cristi worked in FDA Center for Drug Evaluation and Research and Center for Biological Evaluation and Research. She worked as a biologist for the National Cancer Institute.

Rosanna Beltre, Rosanna serves as the deputy director of the Office of Science, Regulatory Project Management. Rosanna has over 14 years of regulatory experience, including 11 at CTP. Within her time at CTP, she has served as a regulatory health project manager and policy analyst.

In these positions, she has focused on policy and program development for all three pre-

market pathways. In her current role, she was responsible for the oversight of regulatory process and review procedures associated with pre-market programs. Prior to working at CTP, Rosanna was a public health analyst at the Environmental Protection Agency.

Yuan Tian, Yuan serves as a director of the Office of Science, Division of Regulatory Science Informatics. Working at CTP since 2011 where she has held various positions, including regulatory health information specialist, data lead, technical lead, and manager. She has played a key role in developing and managing tools and systems to support the regulatory science, evaluation, and approval of tobacco products.

In her current role, she is responsible for the oversight of the development and management of the Office of Science Informatics capabilities, including both infrastructure and operations. Prior to working at CTP, Yuan worked as a health scientist and the Centers for Disease Control and Prevention. Before that, she worked as a computer scientist for

the Oak Ridge National Laboratory.

Johnny Wen, Johnny is the deputy director for the Office of Regulatory Science Informatics in the Office of Science. Johnny joined CTP in 2022 bringing over 25 years of IT experience and system and data architecture application and data modernization, database development, and cloud technologies in his current role providing guidance and oversight in delivering innovative IT solutions and services focused on streamlining the regulatory review process and enhancing productivity within the Office of Science. Before joining CTP, Johnny worked at FDA's Office of Digital Transformation for over ten years.

Prior to his tenure at FDA, he has served as an IT specialist at the Centers for Medicare and Medicaid Services and CMS. We will now begin with our first question, and we will bring our first question from the virtual audience. However, I would like to keep in mind that this mic in the center of the aisle is for any of the audience who is with us face to face to prepare to ask their question.

And our first question for you panelists, with regards to the timing of review, it is stated in this presentation the scientific review will take 180 days. We have seen that review takes longer than 180 days. Do you believe that you will be able to meet the 180-day time frame stated in the presentation in the future?

MS. BELTRE: I'll take that. Can you guys hear me? Perfect. Okay. So I did see during the presentation some people balking a little bit at the 180-day time frame.

And we are going to be honest and state that we have not necessarily hit that time frame in the past. It's our goal to hit it in the future. I do want to clarify when the 180 days starts for PMTA and how it's calculated.

So what you may not have caught is the 180 days is 180 active FDA review days. So this is for when we are kicking off the review. It's actually not from acceptance.

We do have our project managers during first cycle review provide a courtesy call to

applicants so they understand that. If a deficiency letter issues, that will pause the clock. It's no longer an active review day for FDA. And it goes back to the applicant.

If the applicant responds to a deficiency letter, the majority of those have been a -- it's been a major amendment when it comes back which resets our clock for another 180 days. So this is kind of how the clock is coming about. Moving forward, you've seen a couple of presentations today where FDA generally does not expect to grant extensions.

The rationale for this is we are trying to hit our timelines internally and hit the 180 days. We haven't done the best in the past. We're looking at going forward to make sure that our review process is predictable and transparent with respect to any timeline changes.

So with my two cents and with all of my colleagues around me, we are intending to hit the 180 days. It's 180 active review days by FDA based off of that kickoff. And I'm happy to clarify if anything is missing. Thanks.

CDR RUSSELL: Hello, sir. Please state your name.

MR. McKINNEY: Sure. Hi, my name is Willie McKinney with McKinney Regulatory Science Advisors. First, I want to say that the presenters did a really nice job presenting on some very, very tough topics. Greatly appreciate it.

First, I'd like some clarification on something I think I heard. And this is related to flavor ends. So you're only going to look at the presence of information or the absence of information. And so my question is if this is related to youth use, then if the applicant doesn't have an issue, what information are you looking for and why would you look for that information?

MS. BELTRE: So I'll respond to that. The presentation regarding that flavor ends process is just for a small subset. Tomorrow's presentations is going to cover a little bit more with respect to it. However, we are looking at an e-cigarette that contains a flavored e-liquid within it.

The first thing that we're looking for is

usually, like, a randomized control trial, longitudinal, or other information that could show a benefit when compared to tobacco use. And if that's present, we will then open it up to a full discipline review cycle to look at everything that we would traditionally do for a PMTA. If we are lacking that benefit type information, we're not even hitting some of the issues that we need to address youth initiation which is how we could result in a marketing denial. There will be another presentation tomorrow from one of our other individuals in the Office of Science to help address it further. If not, there will be a chance to ask a question in that panel or the final panel with all of senior leadership.

MR. McKINNEY: I wasn't very clear in my question. If -- and I'm a consultant. But if I have a client that sells to an institution where there is no youth use and even FDA has acknowledged that, will you open their application and look for an RCT when maybe they don't need to have one and do that comparison that you're talking about, even if they have flavored products, because no youth access.

MS. BELTRE: So we'll have to look at that specific case. And I don't want to give away any information for a particular applicant that may have a specific population. In cases where we can show that there are no youth use to rise an initiation, that may be what we call other additional information which would take it out to a full scientific review. Sorry for misunderstanding your question. Thanks for the clarification.

CDR RUSSELL: So just to ensure that we answer -- we give fair -- equal distribution to our virtual audience as well as to our face-to-face audience, I'm going to take two in-person questions and then do two virtual questions.

MR. TUCCI: Hi, my name is Mark Tucci. I own Custom Blends for roll your own tobacco. We started in 1993, and we've been made by basically the same company ever since the very beginning.

And so we never -- as a brand owner, I never had to have the recipe information or anything. And my manufacturer, the manufacturer of my brand has always had the recipes. There was basically no reason

for me to have it.

Now that through the -- we did not change our tax characterization from roll your own to pipe tobacco like everybody else did when SJIP hit. And we maintained our status. We were granted grandfather status. And we'd like to use some of our grandfathered SKUs as predicates.

We have been contacted by several large companies. But they back off because I don't have the recipe for my products, and my manufacturer refuses to give me the recipe for my products. And they refuse to give me access to my tobacco -- my TPMF, if there is even a TPMF because they've been making it the same exact way since 1995, this particularcompany. So how would I use my grandfathered products as predicates for substantial equivalents if I don't have access to the recipes?

MS. STARK: Hi, so as you heard from the presentation earlier, data is necessary, right, for a substantial equivalence finding. So in terms of how you can get an SE or receive a positive order, you would have to provide data making that comparison.

It's a one-to-one comparison. Understanding the predicament that you're in, the master file will be the best way for you to maybe get that information to us. And obviously, that's a business relationship issue in terms of working out the details with your supplier or if you're just re-labeling that particular product.

MR. TUCCI: It just so happens that my daughters for the drug manufacturer in FDA compliance. And she was referencing the substantial equivalence like as it occurs in generic drugs where the generic -- who wants to make the generic drug analyzes the predicate and then backs it -- reverses is -- reverse engineers their product into the analysis of the predicate. Can I do that just like they do with Valium or whatever?

MS. STARK: I mean, just a reminder. A lot of our regs may be similar to other centers. But our procedures and our processes and maybe how we conduct our review is different. We have had applicants that sort of reverse engineer products and provide line listing data or studies. And they bridge

that data to make that comparison for the --

(Simultaneous speaking.)

MR. TUCCI: Well, I understand when you're talking generic drugs at a molecular level, you want to have a comparison. But at the tobacco level, do we need molecular comparison to a predicate?

MS. BELTRE: So generic drugs is a little bit different as well because some items are published. You can borrow from that and build on top of it. We don't have that program here in Center for Tobacco Products. What we're going to be looking for is we want to have an understanding that the product is not going to be worse than what you currently have out there. We do have options where we can actually take your case offline and discuss specifics rather than at a public meeting.

MR. TUCCI: Right.

MS. BELTRE: What I do recommend is giving -- we can give a couple of helpful points for why it may be beneficial for your blend supplier to provide a master file to us and provide reference because it's not just beneficial for you. It's also for

others and a way for them to continue the business. We may have a couple of other examples where we could look at a specific case for what you're trying to do. But that may be best served offline.

MR. TUCCI: Well, yeah, okay. Because, like, say, for example, if have a -- if I wanted to look for a different manufacturer, if my current manufacturer says, well, we're just going to refuse to make your brand now, then I'd need to have another manufacturer and I need to find another manufacturer that can do that. And the only way I can really do that is by taking my full flavor and taking it to them and say, can I have a full flavor? Make it as close to this as possible because we're talking burley, oriental, and Virginia -- it's not the whole spectrum of molecules out there to choose from this tobacco. So could I possibly maybe discuss this further with somebody?

MS. BELTRE: Yeah, we actually have project managers assigned for each company.

MR. TUCCI: Okay.

MS. BELTRE: We'll get you the name of

the project manager --

MR. TUCCI: Okay.

MS. BELTRE: -- and have some clarifying questions --

MR. TUCCI: Fantastic.

MS. BELTRE: -- to assist, yeah.

MR. TUCCI: Thank you very much.

CDR RUSSELL: Thank you. Just a reminder, if you do have specific case-by-case situations that you would like to discuss, please contact your regulatory health project manager. Our purpose for this meeting is to really ask the panelists specific questions but not specific questions that would really be so detailed that it's about your particular application. So just please keep that in mind.

Our next question which is actually from the audience. So we have a few shy ones here today. In deficiency letters, will FDA specify whether the correction will start the 180-day period?

MS. BELTRE: So this is the answer you don't want to hear. It's the it depends answer. But I'm going to let you know in general currently the

deficiency letters that we have been issuing have required significant information which has reset the review clock.

As discussed in one of the earlier presentations, if we're looking at new clinical studies, a large analysis of previous submitted data, significant manufacturing and gradient constituent type data, that would in general restart the 180-day clock. So for most of the PMTA deficiency letters, the clock has restarted. Probably not the answer that individual wanted to hear that was shy.

CDR RUSSELL: Well, you kind of touched on this. So I'll go ahead --

MS. BELTRE: Oh, did you have a correction?

CDR RUSSELL: -- and read the next question.

MS. BELTRE: So I do want to hit the correction part of the letter as well. There have been some instances where FDA has inadvertently included incorrect information within a deficiency letter. I want to note that sometimes the correction

does not require significant resources or time from industry.

Sometimes it does. So when we're looking at a deficiency letter going out, I want to remind folks that this is pausing the FDA clock. And it's time for industry to take a peek at.

If we had incorrect values, it's going to require industry to test something completely different. Let's say we list the wrong ingredient that you're actually running a panel on. That will require some time, and we likely will reset the time frame for industry to respond to that letter.

However, if it's something smaller, maybe it's administrative or we misspelled a name, that generally will not reset the time for industry with the 90 days to respond. So I kind of want to note that when we're looking at deficiency letters themselves, we're looking at the content when it comes to reset our clocks. When we're looking at correcting a deficiency letter that FDA issued depending on the content again, if it's going to require significant resources or changes by industry, we do reset that

time for industry to respond.

CDR RUSSELL: Thank you for that clarification. This second question is in line with what we've just discussed in reference to PMTA amendments. Can you give some examples of what may be minor administrative information as not to restart the 180-day period? That 180-day period is very important.

MS. BELTRE: Sure, administrative changes. So let's say that Rosanna Beltre is the authorized representative and she won the lotto. She won one of the major Powerballs that went out. She was hoping for that.

And she has now been replaced by Yuan. That would be something that would come in a letter if we are asking about that that we would not take a peek at and reset the clock. I say that as a funny joke because that's really not what you're focused on.

What we're looking at here is if, for example, we had a question around a clinical study. All of your data is there and it's really just maybe

we misinterpreted something and there's no re-analysis for it and you're placed in that end. That's not going to require a significant amount of FDA resources.

So that, in general, would not reset the 180-day clock. So I'm just trying to show really we're looking at where FDA is spending time analyzing or re-analyzing data. That's where the time is coming in to reset. If we've already done that and maybe we had a slight error and there's no additional analysis needed, in general, we wouldn't reset that clock.

MS. STARK: I would just add that not all typos are created equal. So there's a typo on your data tables. That's very different than a typo in your summary or a typo somewhere else in the application.

So don't -- I don't want you guys to walk away from here being, like, well, minor typo. That wouldn't reset the clock. If it requires a statistician and our epidemiologist to redo an analysis like Cristi mentioned, that typo, although very small, I don't care, 0.02, whatever it is, it

will require re-analysis.

And that requires time. And we want to get it right, right? You can get good and fast. So that's why we need the extra time to do the re-analysis. Thank you.

MR. ROBINSON: Thank you. Good afternoon. Jason Robinson with Juul Labs. A presentation this morning hit on the third queue of review -- or, the third queue with the age verification technology. Can you offer some more detail on that, with respect to maybe how that affects priority of review, or if there are things that manufacturers should do to highlight that in their application or engagement with the Agency?

MS. STARK: I can start. I think that, you know, as we're looking through these applications and, you know, regularly re-evaluating our prioritization strategy, obviously having more information up front for us -- you know, if your application is 6,000 pages, and maybe in the last page you tell us about your age verification, well, that may be hard for us to sift through.

Particularly, in phase one or phase two if we're conducting filing. So, definitely make that known.

There are a lot of different ways that you can let us know, right? You can put it up front, you can request a meeting, you can submit written questions. I would say, definitely make it, you know, your business to actively engage with the Agency as much as you can. Knowing the boundaries and knowing that, you know, it's a lot of work to put together maybe a meeting request in advance. But, obviously age-gating technology is something that we would be interested in. And, as you saw in the queue, is something that we definitely thought about thoroughly, and made that part of our prioritization strategy, knowing that that's something that could be very helpful moving forward.

But, you can add anything.

MS. BELTRE: So, everything Rosa said was accurate. The one thing that I also want to note is, we have, obviously, a new office director, a new center director, we're really engaged in interacting, understanding what works. There may be other ideas

or things that may have missed -- we may have missed when we're considering youth initiation, preventing youth access, things like of those sorts. If you have ideas, please let us know if there's something else we should consider as well. I can't make a promise for what's going to be there, but we are open because you may have ideas we haven't thought of. So, as Rosa said, tell us.

CDR RUSSELL: Any other additional questions from the audience?

Okay. We will now take a question from the virtual audience. Are applicants required to submit their applications according to the seven module structure, or is the seven module structure just a recommendation?

MS. TIAN: Okay, I will take this question. Actually, it's not required but it's highly recommended. Because, the seven module will benefit both, the FDA and the industry, okay? With the standard format, you know, standard table of contents, those kind of things, will help us to develop the automation to identify, extract the

information, and to help with our scientific review process. And that will help you -- some applications, you know, being ready to be reviewed, you know, as soon as possible, too.

So, it's highly recommended. Hopefully, you know, more industry will take this recommendation, you know, in our electronic submission file format in the specifications. Thank you.

CDR RUSSELL: Thank you. So, we have another question from our face-to-face audience. What is the time difference between assessment of SE and PMTA applications?

MS. BELTRE: I'll start, and maybe Rosa wants to join in. We like to tag-team a lot. So, SE has a different time frame, SE is a 90-day cycle. I want to note that, with the SE rule that came out, the timeline also is slightly different than pre-rule.

So, the 90-days is going to start from predicate eligibility, so if an applicant is coming in and they haven't established that their predicate

is eligible -- and let's say they're using a pre-existing, that would head over to the Office of Compliance and Enforcement, they would perform their review. If OCE determines the predicate is eligible, they would give that ruling to the Office of Science, and we would quick off scientific review. That would be the start of the 90 days.

I want to note that we have one potential deficiency letter that can issue after that scientific review, which would essentially stop the clock. Then, upon a response to the deficiency letter or the timeline has passed, we have a second 90-day clock that would start. And we would issue a decision, either, a finding that the product is substantially equivalent to the predicate or not substantially equivalent, at the end.

I'm going to compare that to PMTA. PMTA is 180 days, and that 180 days starts from kickoff. We would then issue a deficiency letter pausing the clock. If it is a major amendment in response to the deficiency letter, we would reset the 180 days and then issue a decision either, granting or denying

authorization for that product to cross into interstate commerce at the end of that 180-day period.

The reason I'm not giving full time periods is, we have had cases with applications where they make it in one review cycle, we've had cases where it's taken two review cycles, we have had to reset clocks, things of that sort. So, it could be as short as 90 days for SE, or it could be the 90 days for SE, the response to the deficiency letter, and the second 90-day cycle. For PMTA, it would be the 180 days, hopefully it's with one cycle, we authorize. If not, we have a deficiency letter, we have the response time frame, and we either, will restart the clock if it's not a major amendment, or if it is a major amendment we restart the clock for the 180 days.

So, I just want to note, for SE it could be two cycles, for PMTA it could also be two cycles. I hope that's helpful. And that's why I'm not giving full time frames for it. Please let me know if further clarification's needed.

CDR RUSSELL: You can come to the floor,

sir.

MR. HOWARD: I'm Chris Howard with Swisher, and I appreciate that insight regarding the time periods. My understanding is that sometimes you -- FDA office complete their review in 60 days, and then only provides 30 days to respond to the deficiency letter. Because, normally most of us I think are accustomed to 90 days to respond for the deficiency letter, and 90 days for you all to review. Are there any -- is there a rationale for when this sort of exception is determined for a collection of SEs, or is this a new thing? My understanding was this was a new policy.

MS. STARK: So -- it's funny, because I was going to add to, sort of, Cristi's summary. For those applicants that have been with us from the beginning, there has been an evolution to the SE program, right, our most mature program. And you have seen, like, this vacillation in time, right. I think at one point it was even 30 days. Thirty days, 60 days, 90 days, right?

So, as we've gained more experience with

the program, become more comfortable, right, you've seen us sort of -- especially for the SE program, you know, it's been around for quite some time. We've taken a lot of actions, sort of hone in on this 90-day timeline. That seems to be much more predictable and helpful on both ends, sort of providing applicants more time, instead of the 30 day or 60 day to response time. And giving our scientific review, you know, ample time to review.

You also have seen that the cycles, if you've experienced any provisionals, have significantly decreased. We had -- in the old DE days, I would say, because I'm a dinosaur here -- we had, you know, applications that went through five, six cycles of maybe 90 or sixty days, with even shorter response time. So, what you've seen is probably the evolution of the program, but consistently we have been at 90 days for quite some time now.

MR. HOWARD: So, if hypothetically -- my company received a notice last week that we -- it's 60 says going in and 30 days to respond to a

deficiency letter. That would be the opposite of the evolution, that would be the de-evolution.

MS. STARK: Yeah, different process, she'll explain.

MS. BELTRE: So, likely that is your predicate eligibility for the pre-existing status. So, there's two different offices that are actually involved in the SE review, and when we're looking at pre-existing status -- what we used to call grandfathered -- so, the product was introduced to the U.S. market, and it was on February 15, 2007, OCE performs that review.

So, they will actually send notice to you and, for that portion of the predicate eligibility, that is 30 days. That's different than the scientific content that you're receiving, so you will continue to see that. And as we evolve to post-rule, you're going to see formalized letters coming from OCE where they're going to have that time frame. If the predicate's eligible, you're then going to be going into scientific review, with the deficiency letters with the time frame from OS.

So, you're seeing a difference in time frame depending on the office. If that's not the case that happened last week, please call me. So, that's what's supposed to be happening -- yeah.

MR. HOWARD: No, this is super helpful. I mean, I think -- if I can build on it -- replying to any deficiency letter in 30 days is extremely difficult. And this certainly jumped off the page that, you know, that could be the reason that you're out. So, that's clearly not, like, the trend, it's not -- it's the opposite, right, it's really the more time to permit for the better review on both sides. So, yeah, hopefully that is the case, Ms. Stark. I appreciate it. And we'll follow up if it's not. So, thank you.

MS. STARK: I also -- just to clarify another point for you, there's a lot of sort of variation, depending on when you submitted and sort of where your application is in the process. You might also find, as Christi mentioned, that post-rule, post SE-rule, those two processes will be sequential. And I think what's a little bit confusing

is that, they're concurrent right now. So, you will see sort of that distinction, right, so you wouldn't -- once you've entered scientific review, which is in the realm of what the Office of Science does, post-rule that should be a little bit more clear.

You'll also -- I think we still have deficiency letters that include both, scientific and Office of Compliance deficiencies. So, if it's unclear to you in terms of, like, is this the right timeline, am I on the right path here, you can definitely ask because there is this transition period where it's going to be very muddy as we move from pre-rule to post-rule.

MR. HOWARD: Super helpful, thank you so much.

MR. McKINNEY: Willie McKinney, McKinney Regulatory Science Advisors. I've heard a lot about age verification technology, has the Agency given any guidance, or do you plan to give guidance, on the data you expect to see for this technology to show that it works? I assume you want to see some data.

MS. BELTRE: So, yes, we'd like to see

some data. I'm going to note, that's outside of the scope for this panel. Wait for tomorrow's presentations, let's see where we're at. It still may not be what you're looking for right now, but we're looking to make available what we can in a timely manner.

CDR RUSSELL: We have a question from our virtual audience. Based on this presentation, Form 4057 appears to have changed significantly after we submitted our application in 2022. Are applicants expected to update this form and resubmit?

MS. TIAN: Yes, okay. I'll take this question. Seeing as the submission did mention it's submitted in 2022, if they take the latest form as of that time, they don't have to resubmit again, okay. But, if you prepare your submission today, please do check the website for the latest form and use the latest form for the submission for now. Anything?

MS. BELTRE: Yeah, I'm going to note, we updated the forms as well as all the guides on our web page, and we provided notice that the effective date for the new forms is today for the PMTAs. So,

we do want to make sure that everyone is aware, brand new Form 4057, as well as 4057(b) with all of the bells and whistles that was presented earlier, those are effective today.

And good news, we've noticed some of you saw it early and submitted early. We thank you for it.

CDR RUSSELL: So, this question is from our face-to-face audience, and the subject is MDO/NSE orders. Can FDA publish redacted NSE orders or MDOs, or consider a web page which list some common application failures that are recent and more timely? The list of common deficiencies have not been updated in some time.

The decision summary page including the TPL summaries is no longer updated with the same frequency as years past. Is a month or quarterly update possible to help regulated industry submit better, more robust applications?

While the FOIA process is a tool that FDA uses and can be incorrect, expensive, or both, publishing information on FDA's website may create

effectiveness for all parties. Looks like my handwriting.

MS. BELTRE: Great job translating that.

(Laughter.)

MS. BELTRE: Okay. So, actually that's a fair question. We have to protect certain information. The names of products that receive negative orders that have not been introduced into interstate commerce is actually commercial confidential information, which requires protection by FDA. As such, we cannot publish that information.

In the past, I do acknowledge that we used to publish a lot of NSE information around the SE program, to help industry understand common deficiencies and other items they need to work for. We can take that back and look at doing that as well for the PMTA program.

With respect to predictability for when we are going to be updating our web page, we used to update it weekly, then every two weeks, then every month -- you're noticing now it's around a quarterly update. We have a lot of materials, we need to make

sure that they are 508 compliant as well. It's our goal to get items out within a quarterly time frame, we're working with our colleagues in the Office of Health, Communication and Education to do this. If you're not seeing things in a timely manner, please let us know. But, we'll do our best to try to get things out on a quarterly manner with updates.

With respect to a list of products that received an MDO, if it has not been made public within -- basically, introduced or delivered for introduction in interstate commerce in the U.S., we can't publish it. But, I do think we'll take back and look at some of the common deficiencies that industry can look at, and potentially putting out a document for that. I can't comment on time frame, but it's helpful and I think something that we can look into. Thanks.

CDR RUSSELL: We do have another question from the virtual audience. Why doesn't FDA use first in, first out in prioritizing SE reports?

MS. BELTRE: It wasn't practical for us to actually use first in, first received for FDA

review of substantial equivalence reports, or PMTAs, due to the sheer volume. With the deeming bolus, we literally received millions in the course of an hour. If we go to look at the electronic record for when they came in, some of them came in at the same time, so we couldn't pick who went first.

In addition, if we were to do the first in, first reviewed, one of the things that could happen is an applicant -- let's say they submitted 10 million products versus another one that submitted two, if they came in two seconds with 10 million products before the one with two -- if we did first in, first reviewed, we'd be reviewing all 10 million products and making a decision before we get to the applicant with two.

When looking at what we could do for fairness, we believed it was best, really, for PMTAs to follow our queue process. We looked at market share to transition to that fully regulated marketplace. And we looked at randomizing by applicant to ensure that, regardless of the size of the applicant or the number of applications they

submitted, they had a fair shot for where they came up with in the queue.

For the SE program, we used the randomization itself. Again, because we received over 6,000 applications in the same time frame and we didn't find it practical. So, we thought it was more fair to actually randomize by applicant and set a number so that everybody would have a bite at the apple, equally.

In the future, when we are back to normal without massive backlogs -- and I promise, that will happen -- we'll see when -- but, I promise that'll happen, it did happen in the past with provisionals with the SE program -- we do intend to get back to first in, first reviewed. A great example that I can show with that is, we went through the deeming bolus and we completed our exemption requests. So, we're actually on time now for our exemptions. So, anybody that is looking at exemption request, you can submit and you're not going to be waiting several years to see that, the queue is manageable for that.

For SE and PMTA, we're getting there. You

saw the progress earlier today, and we're hoping with a plan -- and we'll be transplant on progress -- that we'll get there in the near future. Thanks.

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

Come on up, sir.

PARTICIPANT: Good afternoon, and thank you. Just a quick question. In terms of the phase three in the substantive review, when would the FDA prefer a TPSAC review and how would that affect the entire timing of the process?

MS. BELTRE: So, with respect to TPSAC, it's not required for PMTA. In general, there's two ways to head to TPSAC. Number one, FDA could request a meeting, and it could occur for something that's novel that maybe we would like to get advice on and have public comment. The other option is, the applicant can opt for TPSAC. If that's the case, as noted in the presentation, we're going to want that populated in the Form 4057 with a check mark, put the location for your rationale for why you would like for it to go to TPSAC. We're going to review that

and we'll be in contact with if we agree and would like to go to TPSAC, or not.

With respect to the timing for TPSAC, in general we hold a TPSAC meeting when we have gone through and performed substantive review of the entire application, and generalized and made some of our recommended findings. We would then proceed with our federal register notice, you would be contacted by our DFO for the TPSAC proceedings. And industry plus FDA would have a chance to present, at the microphone, with their findings in front of the Committee for why they believe it's important to be out there for authorization, and then have potential questions asked of the Committee members.

This would, in general, happen during the -- towards the end of the 180 days. In addition, if any inspections or samples are needed for products, this in general would occur after that time frame, as well.

With the need for TPSAC, I will note -- although FDA is trying it's best to hit the 180 days as we're going forward in the future -- depending on

the time and commitment needed from the TPSAC members, it could slightly increase the timeline. That's something that we could discuss with the applicant, and look at that particular product or issue that would need to be discussed with the Committee. I hope that helps.

PARTICIPANT: Perfect. Thank you very much, appreciate it.

MS. FULTON: Hi. Vanessa Fulton with Kleinfeld, Kaplan and Becker. Going back to the substantial equivalent presentation, just a little bit ago discussed a new way to prioritize SE reports. And I was just curious if that's something that's in effect now, if it intends to apply to already pending SE reports, when that will roll out and how that will look?

MS. STARK: I can start. I'm sure Cristi will add. So, the presentation was specific to something we were thinking about. Like I mentioned earlier, the programs have definitely evolved over time and as the context changes, you know, like our policy of first in, first reviewed -- it worked for

a while, then it didn't. I think it's the same for the SE program, right.

In thinking about the number of applications that are still pending -- even though, relative to PMTA, it seems small, it's still a lot. We do want to think about different ways to engage with industry, better ways to prioritize, not just for the applicants but also for the Agency. We want to make sure that, you know, to some level that there's some alignment in terms of what we are reviewing and what the applicant sort of wants us to review. So, something that's under consideration, but it's not effective now, it's not something that we're currently doing.

If you have feedback -- any of you -- on sort of how that process could look better, you know, what about the presentation sort of resonated with you -- that would be really helpful for us to know, as we continue our conversations internally about how to manage the remaining queue for that particular program.

MS. FULTON: And just to be specific,

where would you prefer we direct those questions to? The CTP email, or something --

MS. BELTRE: Honestly, the reality is they'll come through Cristina --

MS. FULTON: Sorry to put you on the spot.

MS. BELTRE: No, it's okay. Pick askCTP, you can, you know, draft a letter to any of our senior leadership that's here. It usually -- there they are. It usually comes through us as folks that are managing, you know, prioritization and the programmatic aspects of those particular programs. So, whichever way is the most convenient, honestly, for you. That's a fair question, and we're thinking about it.

MS. FULTON: Great, thank you.

MS. BELTRE: You're welcome.

CDR RUSSELL: Our next two questions come from the virtual audience. What is the procedure to transfer ownership of a TPMF?

MS. STARK: Okay, I guess I'll take this one. So I guess I'll just talk to that particular question specific to TPMF, but I think the same

process holds true for any of our applications.

In essence, what we need is because we're conducting business with a current owner of that particular file or application, we would want a letter from the owner stipulating that the effective date of the transfer, the terms of the transfer, are you transferring only applications, only TPMFs, only amendments, only of a single application?

Whatever it is, as explicit as you can be in that particular request including the effective date who you're transferring to, providing the contact information of that particular person for the new owner is definitely important. Use company letterhead. Make sure the person submitting the information is somebody that we can conduct business with for your particular company, that it's not just another point of contact, that it's someone that can make decisions on your behalf. These are all the things that we look at when we receive a transfer request.

It is a relatively interactive process. Like if you submit something and you are missing some

information, we will reach out to you and make sure that we secure the information that's needed.

Now for the new company, we also need them to accept their responsibilities of those applications. We do want that information to match. We do want the new owner to -- that that particular individual that you have flagged as someone that you are transferring responsibility to, that they sort of correspond with us and say I accept responsibility, that they've matched the information.

If you're transferring all of your submissions, including amendments, including general correspondences, you can say that, too. That is one way that you can do it instead of listing every single STN if you have a lot of them, but just making sure of the integrity of those two requests, the requests to transfer and the person accepting the responsibility. There's synergy in those two documents and that the information matches. And once we have that, it's relatively quick.

We'll make sure that we're not transferring information to the wrong party, as I'm

sure you guys would be worried about that if we did. So there may be a phone call associated with that particular transfer if there's something we need to clarify but if it's clean, and we've received plenty that have been very, very clean, where there are no questions, then

we process that relatively quickly.

CDR RUSSELL: Thank you. Our next question from the virtual audience, does FDA have a way to allow industry and applicants to receive notification when a guidance is updated, specifically, updates to forms or electronic format guidelines?

MS. BELTRE: So we do have a Listserv that industry can sign up for, for updates that our Office of Health, Communication, and Education manages. They try to also send out tweets and other items when there are updates on the web because you saw many links today with information, in general, for questions around guidances and regulation, effective dates, updates. Your project manager can also be a source for updates as you're calling just

to check on statuses of applications or other clarifying questions.

MS. TIAN: I think Cristi covered the majority of the things and also on the specific web pages, if you want to get a notification of a change, our pages update our changes and you can submit on the top right corner there's a submit button you can just push that button, put your email notification email in there. They will notify you automatically every time the website is updated. Okay.

CDR RUSSELL: Thank you. Do we have any questions of the audience? I have one person right before you. She's coming down. Thank you. We're almost like on the Price is Right, you guys.

(Laughter.)

MS. BOOTH: Hi, I'm Kellsi Booth from Turning Point for ENDS. So we talked a lot about the scientific review period and the time frames there. My question is how long it's going to take to get to that phase for timely filed, non-tobacco/nicotine applications and for totally new products applications going in currently?

MS. BELTRE: For which pathway? Are you looking at PMTAs?

MS. BOOTH: PMTA, yes.

MS. BELTRE: So I know the SE presentation people perked up because they're seeing new ways to look at queues and how we're identifying everything.

For PMTAs, and I was expecting a question going, could you do the same thing there. Currently, we have the three queues that were listed. I believe it was Huda's presentation where we really -- the first queue was the marketplace, where we're going to be looking at market share. We had the top five companies there and obviously, we can look out at some of the sales data now and see that that's changing with time. So right now, we are continuing to look at the marketplace.

We also have the randomization and then we have that third bullet where you're hearing people ask about the age verification technology. And you also heard me say if there's anything else that maybe we need to consider, we could look at that there and for folks that used to hear the old terminology

products of merit, it kind of fell in that category.

With respect to predictability for PMTAs, we have closed over 26 million. But there's still about a little over 500,000 applications left, so I know that there are quite a few companies wondering when it's going to start.

Currently, we are prioritizing closing out what was discussed earlier and many are aware of the suit from the American Academy of Pediatrics which has a deadline of this December. Once that's done, we're looking at kicking off again, notifying applicants for who is in there looking at those three queues.

Really queue one is that marketplace, queue two is the randomization, and queue three is really going to be those novel ones that maybe have the age-gating technology in it or other items. If there's something else we should consider, again, I recommend you raise it to CCP's attention.

With respect to predictability for exactly when your specific application will come up, I can't give that answer right now. What I can commit

to is more transparency for what we're going to be doing in 2024 with putting it out there.

In addition, I can commit to project manager, letting you know the status of it and getting a confirmation from them that they will call you when it's going into scientific review. If there's something buried in your application, as Rosa mentioned, maybe there's age verification buried on one page out of over five million pages, it might behoove you to let your project manager know, submit an amendment, use that Form 4057a, please. Put the original STN in there so we can link it and give us a nice cover page letting us know. That might help you as well with prioritization.

In short, I can't give you a definitive answer, but I'm trying to kind of give you a sense of where we're at and what we're hoping to do. Does that help? I can answer only that far.

MS. ORTEGA: Lillian Ortega with Chemular Consulting, former FDA. Piggyback on the question that Kellsi had which is -- it started out with my thought process is that you earlier today presented

on PMTA metrics as of September 30th of this year. And you also discussed new changes to the acceptance and the filing posed to the PMTA rule. So how does that impact timing as far as acceptance between acceptance and filing? So if an applicant has received an acceptance over a year ago with all of the various changes, what is an estimated timeline or realistic time line for an applicant to receive a filing determination?

MS. BELTRE: So for post rule, we had not -- and I'm being honest, we have not prioritized filing for post rule. This is something that we're talking about, about where that fits in for 2024. We have a couple of other factors for 2023.

My hope, my goal in 2024, is to start to see movement on filing decisions for those remaining 500,000 or so applications that haven't yet gone through. I can't give you a definitive start date. Once we have it though, I am sure someone from the senior leadership team, that will either be Matthew or Brian, will probably give some press around that in the next year.

MS. ORTEGA: Thank you.

CDR RUSSELL: Our next question is from the audience. Now this is a two-segment question. However, I will not read the first segment of the question because it is out of scope at this time However, we will park this question for the panel session on -- tomorrow, Session 7, to allow this question to be asked during that time.

Are companies that submit applications for ingredient change management penalized by CTP's decision to cap a company's review volume to 25 applications?

MS. BELTRE: Okay. So I'm going to reframe the question a little bit for my understanding, just to make sure it's clear.

CDR RUSSELL: I did reframe to the best of my ability.

(Laughter.)

MS. BELTRE: Okay. So the number 25 was actually given in Chris' presentation where we're talking about the proposed cap of 25 products kicked off and that's per team, when we're discussing some

updates to the SE prioritization.

I want to note that when we were discussing the proposal for SE, we do understand that some manufacturers may have hundreds of applications submitted. And when we're talking about prioritization, we're also looking for some industry engagement to understand what's important to them. If there are 50 products, let's say that they use the same predicate, that predicate is eligible, and it's the same modification, and when I'm saying same, I mean identical. I don't mean there's 70 changes. I mean it's an identical modification. It behooves industry to let us know.

Twenty-five, I'm going to say, is in general. I'm looking at my Division of Product Science, Colleen, she's over there. She actually sets the final number for her staff. But I do think there's a little bit of wiggle room if it is an identical modification using the same predicate because we're really looking at that one comparison for that modification. So there's no penalty if we go further than that.

There's also no penalty when we're setting a cap at 25. We're really looking at predictability for our review time frame. For us to hit 90 days, we understand that a one-to-one comparison takes our review team some time to dig through the data and do their own independent analysis to arrive at their recommendation. Twenty-five seems to be that number. In the past, actually earlier this year, it was 20. So you can see there is some increase for that over time. But with a little bit of engagement, we're willing to wiggle that number a little bit more.

What's important though is really understanding what's most important for review by the applicant. So for example, if you have let's just say a post-deeming bolus product that you really want to introduce to the market and that's your top priority, you should let us know so that we make sure that we understand your motivation and maybe we can try to hit what's important to you first for review so you can get answers and make some decisions within your own company for moving forward. So I hope that

helps. If not, they can submit another question since they're anonymous.

CDR RUSSELL: Thank you, our next question comes from the virtual audience. Now that some ENDS products have been approved via PMTA, is it possible that an SE can be achieved for ENDS products that are similar?

MS. STARK: No.

(Laughter.)

MS. STARK: I'm very succinct. The criteria for a predicate for the SE program is you have to be either grandfathered or previously found SE. Although PMTA is a higher bar, that is not how the regs are structured, so therefore, you cannot serve as a predicate for the SE program.

MS. BELTRE: So Rosa's succinct and this is why we love her. I'm a little bit more verbose, so I'm going to give another option for this individual that's looking at these authorized ENDS out there and how they may be able to modify and come in.

We have what we call a supplemental PMTA

where basically you could modify that product, submit a supplemental PMTA for those modifications to look at authorization. This really is for the applicant that received the authorization for the PMTA. It's not for someone that doesn't have the rights to it, so I want to note that. That's a little bit different than the SE program, but I want to note that option is out there.

The second option that is out there for the applicant is an exemption request. So the exemption request can be a minor modification to any legally-marketed product. So let's just say that you are completely removing a characterizing flavor and you just have tobacco. Let's say before it was tobacco cherry and you're going to tobacco. I'm going to recommend that you may want to speak with us beforehand because right now we're looking at youth. That would be something we want to discuss, but I'm giving an example of where you could have an additive change and you could look at another program for that.

So when you're looking at something that was authorized under a PMTA, you actually have two

options. You have a PMTA or you have an exemption request pathway.

CDR RUSSELL: Thank you. Do we have any additional questions from the audience? We do have -- thank you.

MS. HO CHEN: Angela Ho Chen, independent consultant, FDA Regulatory and Legal Services.

This might be a very basic question and it will give you kind of a feeling for the spectrum of applicants out there. In terms of notifications or notice, using the regulatory and legal term, for FDA forms, what is the proper notice? Is it the website? Is it -- and I'm dating myself, the Federal Register, or is it something else?

MS. BELTRE: So I don't want to date myself because I remember notice was when you would actually walk into the Federal Register Office, open up the book for what was going to publish the next day, and you could have notice that way, but it was the formal posting the next day that constituted notice and I just did date myself. That's okay.

I want people to be aware that there are

multiple ways that we can notify the public. Federal Register is one such way. There can be notification to the public through a forum such as a hearing. There can be ways to notify through our website. There can be ways to notify through statements, through some of our senior officials. So it's really a larger bucket than what was in the past. I know that FDA has a lot of other ways to outreach, so I would use all of the above.

If you're looking at the notice for our current forms with when they were out there, we actually had a formal form update on our website over 30 days ago where the forms were updated for the Form 4057 and 4057b. Shortly after that, we then provided updates on the CTP website to point back to the OMB website to give some updates with respect to that, as well as to provide links to helpful documents and our new validator tools so that you guys can actually see what our systems are looking at in order for our applications to ingest.

So I just want to note that the OMB update that occurred initially with the form was really that

first notice because that's where it goes through, but we did follow through in the next week on our website with our updates, if that helps. Great.

And for people that have been around, they no longer have the open book in the Federal Register Office. We've gotten away from that paper, just in case you go to look for it.

CDR RUSSELL: Do we have another question from the audience?

Shy bunch here today. I will read a question from a virtual audience and I'm going to paraphrase this question. Based on the path on the last presentation surrounding SE, it is my interpretation that if an application was submitted post-2020, it has not advanced into the queue for scientific review. Is that correct?

MS. STARK: Yes. That is correct. My final answer.

(Laughter.)

CDR RUSSELL: Okay. We have another question from the virtual audience. For PMTAs that are still under review, how should submitters inform

FDA of changes, for example, a change in authorized representative or addition of manufacturing locations that were not previously included in the applicant's 4057a?

MS. BELTRE: So forms are our friends. I do say this a lot to my staff. They laugh and they roll their eyes. Actually, they might be doing it on the panel as well.

A brand new amendment, submission of Form 4057a, we would really appreciate if it is pre-rule. It's not required, but it would really facilitate our review. Post-rule, it will be required, so any application received November 4th, 2021 or later, you need to utilize Form 4057a.

As a reminder, you need to state that is an amendment. You need to actually give us the STN that you are amending. You can see that in CTP portal. If it's not viewable, you can ask your project manager, you can submit a question to Ask CTP. We have a myriad of ways to get you that STN to make sure it's in there. If we don't have that STN number, we can't infer, and it won't be reviewed.

The other thing I want to note is give a courtesy call to your assigned regulatory health project manager. They'd like to know what's coming in. They'd like to know if there is any updates to contacts, if there are any updates to sites, or authorized representatives. They can also help walk you through the form if you need to submit it. So please tell us.

CDR RUSSELL: Our next question is from the virtual audience and I'm going to paraphrase this question as well. And I'm going to leave out a portion of this question because it has been already answered previously. Straight to the point, has FDA increased staffing of reviewers to handle the backlog of SEs?

MS. BELTRE: So I'm going to say that's a little outside of the scope and I'm going to punt that to Panel 7 tomorrow for our office director.

(Laughter.)

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

If not, I will read our question from the

virtual audience. How does FDA anticipate requiring implementation of the new submission requirements and will this be via eSubmitter or a different new application?

MS. TIAN: I will start this question. Maybe Johnny can chime in or Christi, you can chime in later.

So all the new submission requirements we mentioned today, actually, it's not a request. It's just a recommendation. We don't have binding guidance or rules to make it mandatory. So in order to make all these changes appear on our IT system, we don't need the summary rules and the policies to enforce it and so that we can do in our system, make it required.

So as of now, we will look into, you know, in the future, to develop some guidance and the rules to make all this kind of IT summation request changes happen in the future, but we are open to any feedback and suggestions on this, too.

MR. WEN: Yes, to add on to what Yuan just said, we also are looking at the process of modernizing our eSubmission process, you know, with

CTP portal and with eSubmitter will probably be combined to one, there won't be a separate application to download in the future. So we're also constantly modernizing stuff, but the whole idea is to really make the whole submission process easier for industry and for the reviewers, right, to make it easier for us to review, receive the submissions.

MS. TIAN: Just want to add one more point. FDA just announced I think last year about the FDA has an effort to modernize the electronic submission gateway, the new ESG Next Gen project. So the new release, the first release will be coming soon next year. The new modernized tools may help for the electronic submission, too.

CDR RUSSELL: Do we have any additional questions from the audience? If no additional questions, I would like to read our last virtual question and I will paraphrase this one as well. It was stated today that, in general, extensions for SE will not be granted. However, assuming that there is a reasonable consideration and rationale for a scientific justification of why an extension for the

90-day window of a deficiency letter more time is needed, would FDA be open to granting that additional time?

MS. BELTRE: So we've been using qualifying statements where we say in general, we do not intend to grant extensions. There may be some sort of extraordinary circumstance where we may need to grant an extension. We had an unfortunate circumstance about three years ago at the start of COVID with the borders being shut down. Things could not be shipped. People could not test. People had to report home.

We've had natural disasters where we have had fires, hurricanes, floods, other types of issues that have also warranted a reasonable request for an extension where that was the site that was impacted. So in general, we don't intend to grant extensions, but there may be circumstances where an extension could be warranted, so we will review the rationale and respond accordingly in writing. Thanks.

CDR RUSSELL: Unfortunately, this is not our last question. So we have approximately four

minutes left for our question and answer period, so we will try to fit these last questions in as much as possible.

This is from our virtual audience. Did you state earlier that you were currently not receiving -- that you are or are not reviewing exemption requests?

MS. BELTRE: We are reviewing extension requests so the nice thing is we don't have a backlog. Those are going to be famous last words because I'm waiting for a deluge starting tomorrow, but as of today, we are up to date with our exemption requests, so we are currently reviewing exemption requests. If you have a question or you haven't seen movement, please contact your regulatory health project manager so that we haven't missed anything. Thanks.

CDR RUSSELL: Our next question is from the audience. How is synthetic products for PMTA incorporated into the queue for filing of PMTAs?

MS. BELTRE: So the authority for non-tobacco derived products came with new legislation. As discussed, I think it was Eric's presentation, we

prioritized those that were part of our what I'm calling our NTN bolus in a specific transition period and those were really the applications that were submitted through May 14th of that year and received that date, and he actually had an explanation of physical receipt versus electronic receipt. It was Eastern Time here because that's where we're located.

We have moved the one percent of those in that bolus that were accepted. Some have gone into filing. Once we get through the current priorities for this year, including some of the outside sources such as AAP, we're planning to look at that.

With respect to those that were submitted and received outside of the NTN bolus, those are not included in that prioritization. They're going to be discussed, as we're discussing the PMTAs as a whole. And remember, we have those three queues where we're looking at the market place, the market share. We're looking at randomization and we're looking at the novel products with age gating. And it would fall into one of those three queues currently.

CDR RUSSELL: Do we have any additional

questions from the audience?

There is a question that has come in from the audience. However, I am going to paraphrase the question so that we do not spend an extended amount of time just reading out the question.

Is it possible for a company to understand where they are in their product scientific review process? If they are in scientific review and have answered a deficiency notice and now are just waiting, can they understand what has been reviewed to date?

MS. BELTRE: I'm thinking through the queue for who has actually gone through first cycle review, we've issued a deficiency letter, and we haven't kicked off. So the first answer is contact your RHPM, but I do understand our RHPMs are gestating under review. Some applicants have then contacted myself, or Rosa, or the Associate Director Anne Radway. We're the three that preside over the RPM.

What I can say is if there are questions, what we can do in the RPM is let you know specifically are you currently under review or not. So for an

applicant that has already gone through first cycle review, received a deficiency letter, not received a deficiency letter, they have that notification, they want to know where they're at, the PM can answer if they're actively under review or not.

If there are further questions, likely it will take a little bit longer because we're going to look at the facts for the case and let you know where you're at, but my goal is transparency, so you know where your application stands. And I think it's better to hear that you're under review with the review team or you're sitting in queue waiting for us to kick off. And I'm committed to letting you know that.

So please follow back up and we will get a response to you.

CDR RUSSELL: Do we have any additional questions from our face-to-face audience, as well as our virtual audience?

We do, however, have one question that has come in from the virtual audience. However, this question is more appropriate for Panel 7 and so we

will postpone that question until tomorrow.

If we have no further questions, this concludes the panel session of our public meeting today. Thank you, panel, we appreciate all of your questions.

(Applause.)

Thank you to our virtual audience as well as our face-to-face audience for asking those questions and just putting our panelists on the spot. We really appreciate it.

Without further ado, I would like to, before I leave you today, I would like to introduce Dr. Todd Cecil. He is the Deputy Director of the Office of Science and he will do our closing remarks. So Dr. Cecil.

DR. CECIL: Thank you, Avena, I appreciate it. As I stand between you and the beltway traffic, I would like to take as long as possible. We can make this about 6 o'clock before we're done.

So I actually would like to thank you very much for your in-person attendance and those of you who are watching on the cameras, thank you so

much for tuning in. I think we had over 400 people online today. We have about 200 people here in person and so we're really thrilled to have all of you here.

I want to thank the speakers and the panelists today. There's been a lot of information that's been provided, some great questions. We really like Rosa's answers and I'll try to use that more often when she asks things of me.

I would like to go ahead and close out the first day of the meeting with an announcement for tomorrow. We begin at 8:30 back in here, so we'll have a little bit longer day tomorrow and we will have an opportunity to speak to you about general topics in Session 7.

If you have questions you did not get answered or you think about them tonight over an adult refreshment, which I suggest to all, go ahead and send them to the Ask CTP and we'll go ahead and try to see if we can get them on the agenda for Session 7.

With that, I want to say thank you so much, have a wonderful evening, and be careful out

there.

(Whereupon, the above-entitled matter went off the record at 3:53 p.m.)