UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

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April 6, 2017
8:30 a.m.

Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, MD 20903

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M E E T I N G

(8:30 a.m.)

DR. HUANG: I'm Phil Huang, Chair of the Tobacco Product Scientific Advisory Committee. Want to welcome everyone and thank you for joining us.

First, I want to make a few statements, and then we will introduce the Committee. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topics at hand take place in the open forum of the meeting. We're aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media

until its conclusion.

Also, the Committee is reminded to please refrain from discussing the meeting topics during the breaks.

Thank you.

MS. COHEN: The Center for Tobacco Products of the Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the Federal Advisory Committee Act of 1972 and the Family Smoking Prevention and Tobacco Control Act of 2009. The Committee is composed of scientists, healthcare professionals, a representative of a state government, a representative of the general public, *ex officio* participants from other agencies, and three industry representatives.

With the exception of the industry representatives, all Committee members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with applicable federal ethics and conflict of interest laws is being provided to participants in today's meeting and to the public.

The purpose of today's meeting is to educate Committee

members on processes used in the review of tobacco product applications exclusive of any particular products or class of products and is not to seek advice on a regulatory decision or action. Therefore, this meeting does not involve deliberation, decision, or action that is focused upon the interests of specific persons or a discrete and identifiable class of persons; and accordingly, it has been categorized as a meeting involving a non-particular matter.

Based on the characterization of this meeting as involving a non-particular matter, all voting members of this Committee have been screened for potential conflicts of interests as per Section 917(b)(1)(C) of the Food, Drug & Cosmetic Act. Section 917(b)(1)(C) of the Act states that voting members of TPSAC shall not during their tenure on the Committee, or for the 18-month period prior to becoming such a member, receive any salary, grants, or other payments or support from any business that manufactures, distributes, markets, or sells cigarettes or other tobacco products. Voting members were thus screened accordingly.

Based on the agenda for today's meeting and the interests reported, FDA has determined that the screened participants are in compliance with Section 917(b)(1)(C) of the Act.

With respect to the Committee's industry representatives, we would like to disclose that Drs. William Andy Bailey, William McKinney, and David Johnson are participating in this meeting as non-voting representatives. Dr. Bailey is acting on behalf of the interests of the tobacco growers. Dr. McKinney is acting on behalf of the interests of tobacco manufacturing industry. And Dr. Johnson is acting on behalf of the interests of the small business tobacco manufacturing industry. Their role at this meeting is to represent these industries in general and not any particular company. Dr. Bailey is employed by the University of Kentucky. Dr. McKinney is employed by Altria Client Services. And Dr. Johnson is employed by National Tobacco Company.

I would like to remind everyone present to please silence your cell phones if you have not already done so.

I would also like to identify the FDA press contact, Michael Felberbaum. If you are here, please stand up. And there he is. Thank you.

DR. HUANG: Okay. All right. Now we will take the time to have everyone introduce themselves at the head table. We can start with Dr. Johnson.

DR. JOHNSON: I'm David Johnson. I am representing the

Small Tobacco Manufacturers Association, and I'm employed by National Tobacco Company.

DR. BAILEY: Andy Bailey, University of Kentucky, and I'm here to represent tobacco growers on this Committee.

DR. McKINNEY: Morning. I'm Willie McKinney, Vice President of Regulatory Sciences at Altria Client Services, and I represent the tobacco industry manufacturers.

DR. WANKE: Morning. I'm Kay Wanke. I'm at the Office of Disease Prevention at the National Institutes of Health.

DR. KING: And I'm Brian King. I am with the Office of Smoking and Health at the U.S. Centers for Disease Control and Prevention.

DR. CAMPOPIANO: And I'm Melinda Campopiano. I'm a family doctor and addiction medicine specialist, Chief Medical Officer for the Center for Substance Abuse Treatment at SAMHSA.

DR. GIOVINO: Hello. I'm Gary Giovino. I'm with the School of Public Health and Health Professions at the University of Buffalo.

DR. BIERUT: Hello. I'm Laura Bierut. I'm from Washington University in St. Louis and a researcher in genetics of addiction.

DR. O'CONNOR: Richard O'Connor. I'm a professor at the

Roswell Park Cancer Institute, and I study tobacco use and health behaviors.

MS. COHEN: Caryn Cohen, Designated Federal Official for the TPSAC.

DR. HUANG: And I'm Phil Huang. I'm the Health Authority and Medical Director with Austin Public Health Department.

DR. FAGAN: Pebbles Fagan. I'm a professor at the College of Public Health, University of Arkansas for Medical Sciences.

DR. THRASHER: Jim Thrasher from the Arnold School of Public Health at the University of South Carolina.

DR. MERMELSTEIN: I'm Robin Mermelstein. I'm a professor of psychology and the Director of the Institute for Health Research and Policy at the University of Illinois at Chicago.

DR. OSSIP: I'm Deborah Ossip, and I'm a professor in the Department of Public Health Sciences at the University of Rochester Medical Center.

DR. WEITZMAN: Hello. I'm Michael Weitzman. I'm a professor of pediatrics and environmental medicine at the NYU School of Medicine and a professor of global public health at NYU's School of Public Health.

DR. ASHLEY: I'm David Ashley. I am a Senior Advisor in the Office of the Center Director at CTP.

DR. HOLMAN: Matt Holman, Director of the Office of Science at FDA's Center for Tobacco Products.

DR. CHEN: Ii-Lun Chen, Division Director for Division of Individual Health Science in the Office of Science, Tobacco Products.

DR. APELBERG: I'm Ben Apelberg. I'm the Director of the Division of Population Health Science at CTP's Office of Science.

DR. HUANG: Great. So now we'll hear from Dr. Ashley.

DR. ASHLEY: Well, thanks. First thing, I just want to welcome everybody who is in the room attending and also those who are connecting remotely. Thank you for coming to this TPSAC meeting.

On a personal note, if you have not heard, I'll be leaving FDA in May. Dr. Matthew Holman has already moved into the position of the Director of CTP's Office of Science.
Dr. Holman has a long history already at CTP, and I have every confidence in his ability to continue the work that goes on in the Office of Science, and I'm going to let Matt describe more about his background for just a few minutes when he gets up and presents himself.

TPSAC last met April 9th and 10th of 2015 to review and

provide advice to CTP on the Swedish Match North American MRTP application. Since that time, CTP has weighed the information provided in the application, the information provided by the public, and advice from TPSAC, and has provided responses to Swedish Match on those applications.

Because it's been so long since the last meeting and that PMTA and MRTP decisions have been made by FDA during that time, also because we have many new members who were not on the Committee during the last meeting and we are expecting in the near future to receive significantly more PMTA and MRTP applications which will be referred to TPSAC, we believe it's worthwhile to bring TPSAC together.

And the purpose of this meeting is to discuss the processes that are used in review of tobacco product applications, the statutory standards applicable to different types of applications, the scientific basis for review decisions, focusing on PMTA and MRTP, and the role of TPSAC in the review process. We believe by having this meeting now, we will better prepare TPSAC to play their part in the process.

This meeting is primarily about PMTA and MRTP. TPSAC has a statutory role in MRTP review and, when it's appropriate, also has a role in PMTA review. So those applications are the

focus of this meeting.

Substantial equivalence will be discussed by FDA but only in the overall context of marketing decisions. We want to really try to kind of give you an overview of everything, so that's why we've included SE. The meeting is not about SE, and TPSAC will not be asked questions about SE.

In addition, CTP is not asking TPSAC to review or comment directly on FDA's decisions related to the Swedish Match MRTP application, but that application serves as a really good example for us to use to discuss the process we went through in the past, what worked well for TPSAC and where improvements can be made.

So let me emphasize again this is about how we can improve the process of involving TPSAC in the PMTA and MRTP review process. We believe it'll make the process for TPSAC review as effective and efficient as possible. It'll benefit FDA, the applicants, and public health for us to go ahead and discuss the process and how we might make those improvements.

And with that, I will hand it over back to Dr. Huang.

DR. HUANG: Thanks, David.

So next on the agenda, I think we are going to hear an overview of product review pathways from Dr. Holman.

DR. HOLMAN: Good morning, everyone.

Just briefly, a little bit about myself real quick before I start here since I don't know all of you. I've been in FDA for 15 years, a little bit more than 15 years. I spent almost a decade working on over-the-counter drug products in FDA's Center for Drug Evaluation and Research.

I've been at CTP for a little more than 6 years, served as the director for the division responsible for chemistry, engineering, and microbiology. In addition to that role as division director, I also served in a broader capacity as the technical project leader, TPL, for SE program. So that's just sort of a little bit about me.

I will say also that David and I have been working together for a number of months here to hand off the office director position and ensure a smooth transition. So by the time David leaves in May, you know, I should be running at full speed.

So with that, let's turn to the topic of conversation today. So my colleagues are going to delve into a little bit more detail in each of the application pathways later today. What I want to do is just give you sort of the broader, big picture, frame up their conversations so you can see how all

these different pathways are similar and dissimilar to one another before they get into, a little bit more into the details of each.

There are four application types: exemption request, substantial equivalence or SE reports, PMTAs, and MRTPAs. We're not really going to talk that much about exemption requests and SE reports, but for completeness so that everyone understands our marketing application programs, we're going to at least touch a little bit upon those two and really focus on PMTAs and MRTPAs.

Regardless of which of these four application types we're talking about, our premarket review within CTP is based upon the best available science. We are a science-driven organization, and we look at the science in all these application types. So that's one of the commonalities across all four types.

The applicant -- and again, in all four application types, it's the responsibility of the applicant to provide adequate evidence for FDA to make a filing decision. Now, that being said, FDA does look at all the available science. We do often look outside the application if we think there's other available science that would inform our decision with regard to

any of these application types.

Again, the overall goal here, and this is really my big takeaway I hope that you walk away from my talk with, is regardless of the application type, we are looking at what is the overall net impact to the population.

So we look at factors, such as never users: Do they, you know, are they more likely to begin using a tobacco product if we were to allow marketing of a certain tobacco? We look at former users, issues such as are they likely to reinitiate use of tobacco products? We look at product toxicology: What is the harm caused to product users and nonusers by tobacco products? Lastly, we look at patterns of use: Are users of tobacco products likely to increase, or increase or decrease use, move towards cessation or not? So, again, we put all these factors together to say what is the overall net impact on the population by allowing marketing of a given tobacco product.

Now, what I want to do is kind of explain to you -- this slide is a little bit confusing, so I'm going to walk through it, but the goal here is just sort of explain to you what does it take to get a tobacco product on the market. The way we look at it, or I think the way it's easiest to think about is

when was the product first introduced to market.

So all those products that were on the market as of February 15th, 2007, and this is assuming they have not made any changes to those products that were on the market as of that date, we call those or define those as grandfathered products. Those products are allowed to stay on the market. They don't require -- there is no requirement for the manufacturer to submit a marketing application to us. They can just stay out there and market. There are other requirements that manufacturers have, but they do not need a marketing order from us to continue to market those products.

The next group of products are those that came on the market right after that time up until February -- or excuse me, up until March 21st of 2011. These are new tobacco products by law. They're referred to as provisional tobacco products. Manufacturers of these products were required by March 21st of 2011 to submit SE reports to us that we refer to as provisional SE reports. As indicated by the little traffic light here on the right, those products are allowed to stay on the market unless FDA issues an order finding them not substantially equivalent.

And then lastly, products on the market after February

16th, 2007, up until present day that are not provisional tobacco products, those are new tobacco products, and they could come in -- we could receive an application from manufacturers that will either be a PMTA, SE report, or exemption request. Depending on the specifics of the product, the manufacturer would choose the most appropriate marketing pathway. Those products cannot go on the market unless FDA issues a marketing order allowing them to be marketed.

So now I want to shift over to MRTPA. It's a little bit different. The SE, PMTA, and exemption request, those are really pathways to get a product on the market. MRTPAs are really an application type to be able to advertise a product as modified risk. So it's not really an application on a product on the market. It's really an application to identify a product as a certain thing, which is a modified risk.

So if we have a grandfathered product -- again, these are ones that were on the market as of February 15, 2007 -- they only require one order from FDA to be marketed as a modified risk product. And that is just really the MRTPA order that we would issue.

For provisional products, if they would like -- if the manufacturer would like a modified risk -- to identify that

product as a modified risk product, they would be required to submit a provisional SE report as well as an MRTPA. However, they would only require an order under the MRTPA to be able to identify that product as modified risk assuming that FDA had not issued an NSE order for the product under the provisional SE report.

And then, lastly, all other new products would be required to submit, again, either a PMTA, an SE report, or an exemption request as well as an MRTPA. And they would in this case need two orders. They would need a marketing order under the PMTA, SE report, or exemption request as well as an order under the MRTPA.

So now I'm just going to touch on each of these application types in just a little bit of detail because, again, my colleagues would go into more detail throughout the rest of the day.

SE reports are a comparison of new and predicate products. More specifically, it's a comparison of the characteristics of the new and predicate products. I've listed here on the slide what some of those characteristics are, but you can see it's a fairly detailed identification of the new and predicate products that FDA would get in an SE report.

And then FDA looks at really two things. There are two standards basically to issue an SE order under this pathway. The first is: Are the new and predicate products, do they have the same characteristics as one another? If they do, again, we could find them substantially equivalent and issue a marketing order.

The other scenario is that the characteristics of the new and the predicate product are different. Then we ask the question, do these differences in characteristics raise different questions on public health from the new product in comparison to the predicate product? If they do not raise different questions of public health, we would issue a marketing order.

Exemption requests are very similar in some regards to SE reports, but they're much narrower in scope. Again, it's a comparison of a new and original product very similar to SE report, but the types of differences between the new and original product are much more limited in scope than an SE report.

These types of applications can only be submitted if the change between the new and the original product is to an additive. The change also has to be minor. And the applicant

has to demonstrate that a full SE report is not necessary to ensure permitting marketing of that tobacco product is appropriate for the protection of public health. And the applicant also has to demonstrate the exemption is otherwise appropriate.

So now I'll turn to PMTAs. I've listed on the slide here the information that's required in a PMTA. You can see it has a lot of the same information we get in an SE report, but there's also a lot of additional information that we would get on our PMTA not included in an SE report, such as proposed labeling is a requirement in a PMTA.

Here, what we're looking at is would the marketing of the product, the subject of the PMTA, be appropriate for the protection of public health? So what that means is we look at things like what are the risks and benefits to the population as a whole. This, again, would include users and nonusers of tobacco product. In terms of appropriate for protection of public health, we'd also look at the likelihood of the impact on cessation. We'd also look at initiation.

So, lastly, I'm going to turn to MRTPAs. Again, as I stated earlier, this is not an application to get a product on the market. Rather, it's an application to identify a product

as reducing the harm or risk of tobacco-related disease.

And there are really two types of order in the statute. The first is a risk modification order. This type of application, essentially, the applicant is asserting that their tobacco product will reduce the risk of some disease or some disease endpoint.

The second type of MRTPA application is an exposure modification. I've shown an example here on the slide just for illustration purposes, but this is really stating that the tobacco is going to reduce the exposure of, for example, a toxicant to the users and potentially nonusers.

Again, here I've listed what will be included in an application. It's somewhat similar to PMTA in terms of the level of detail but again focused more on the risk modification or exposure modification that the applicant is asserting.

So, lastly, just to sum things up, again, no matter what the application type, FDA gets certain information that we look at on the subject tobacco product and, in some cases, on a predicate or original tobacco product or other comparable products on the market. We then look at what impact marketing that product would have. We look at factors such as toxicity, consumer perception, pharmacokinetics. And then we pull all

that information together ultimately to look at how does this affect morbidity and mortality associated with the tobacco product.

So, in conclusion, again, no matter what the application type, whether it be exemption request, SE report, PMTA, or MRTPA, FDA's goal is to protect the public health and to look at how the products under any of those application types would impact public health.

Thank you for your attention.

DR. HUANG: Thank you, Dr. Holman.

Are there any questions anyone has for Dr. Holman?

(No response.)

DR. HUANG: Thank you.

Okay. Next we're going to hear from Dr. Poddar on the substantial equivalence pathway, an overview of that.

DR. PODDAR: Good morning. My name is Atasi Poddar. I'm a senior regulatory health project manager at the Office of Science of Center for Tobacco Products.

The focus of my today's presentation is to give you an overview of the substantial equivalence pathway. During the presentation, I will explain the definitions and statutory framework. I will discuss the review process from start to

end. And finally, I will discuss how FDA applied the statutory standard of substantial equivalence in its review.

Okay. Section 19(a) of the Federal Food, Drug & Cosmetic Act, which I'm going to refer as FD&C Act, provides the definition of substantial equivalence. The term "substantial equivalence" means the new product has the same characteristics as the predicate tobacco product, or the new product has different characteristics than the predicate product but the differences do not cause the new product to raise different questions of public health.

The term "characteristics" is defined in Section 19(a) of the FD&C Act. It means the materials, ingredients, design, composition, heating source, or other features of a tobacco product.

A predicate tobacco product is a product that was commercially marketed in the United States other than test markets as of February 15, 2007. We also refer to it as grandfathered product. A predicate product could also be a product that was previously found to be substantially equivalent by FDA.

The primary pathway for obtaining a marketing order from FDA is a premarket tobacco application. It is discussed under

Section 19(c) of the FD&C Act. The substantial equivalence pathway is an alternative to the PMTA pathway.

According to Section 19(a), the manufacturer of a new tobacco product is not required to obtain an order under PMTA if the manufacturer has submitted a report under Section 905(j), and the Secretary has issued an order that the tobacco product is substantially equivalent to a predicate tobacco product that was commercially marketed in the United States as of February 15, 2007, and the new product is in compliance with the requirement of this Act.

Now let's take a look at Section 905(j), which provides the time frame of industry submission and the basis for substantial equivalence. To get a marketing order under substantial equivalence pathway, the applicant will submit a report to FDA 90 days before introduction or delivery for introduction of a new product into interstate commerce for commercial distribution in the United States.

The report will contain the applicant's basis for determination of substantial equivalence, which includes the rationale and data to prove the new product is substantially equivalent to the predicate product and the new product is in compliance with the requirements of the FD&C Act.

There are two categories of SE reports. One is a provisional report, and the other one is a regular report. A provisional report arises from a special provision of the FD&C Act. To be considered as provisional, the tobacco product must have been introduced into commercial distribution in the United States between February 15, 2007, and March 22nd, 2011, and an SE report was submitted by March 22nd, 2011. A provisional product can remain on market unless an order has been issued that the product is not substantially equivalent to a predicate product.

Any product that does not fit the criteria of a provisional product is a regular product. To legally market a regular product, the manufacturer must obtain a substantial equivalence order from FDA.

Now I'm going to talk about prioritization of review of SE reports. We have given priority to the review of regular SE reports. Why? It's because the regular products cannot be legally marketed without a marketing order from FDA. The review of regular reports starts immediately upon receipt of a report.

I have mentioned before that a provisional product can remain on the market unless FDA issues an order that the

product is not substantially equivalent to a predicate product. FDA received a large number of provisional reports by the due date of submission of provisional report. It was not practical for us to start review of all those reports simultaneously. Therefore, it was important for us to identify the provisional products that may have the greatest potential to raise different questions of public health.

How did we identify those products? We have conducted public health impact review, or PHI review. A PHI review is a review of limited key product attributes to determine the relative potential of the provisional product to raise different questions of public health.

I would like to emphasize here that a PHI review is different from substantial scientific review of all information submitted in an SE report. The substantial scientific review is conducted at the scientific review phase.

Now let's look at some of the criteria that we have used to identify the provisional products that may have the greatest potential to raise different questions of public health. One such criteria was if the new product was a nonconventional product.

Now, the design features or the composition of a

nonconventional new product could be different from the predicate product, and the differences may raise different questions of public health. One example of such nonconventional tobacco product is a cigarette that contains a bead that can be crushed to release the contents.

Our other criteria was inadequate characterization of either the new or predicate product. In some of the applications, we noticed that the new or the predicate product was not identified by product category, subcategory, package type, or product quantity. So, in those cases, we could not determine which new tobacco product was compared to which predicate product. And therefore, we determined that those new products may raise different questions of public health.

In some applications, the new product was from a different category than a predicate product. For example, a cigarette was compared to a smokeless product. In those cases, we determined that the differences in composition, design features, or heating source of the new and predicate products may raise different questions of public health.

In addition to the criteria I have discussed, significant differences in characteristics, like an increase in total alkaloids or total bases or increase in harmful and potentially

harmful constituents, significant decrease in acidic ingredients, or significant differences in tobacco blend or design features were also considered some of the criteria for identification of provisional products that may have the greatest potential to impact public health. Based on PHI review, the review of provisional report was prioritized.

Now I'm going to discuss our review process from receipt of an application to issuance of decisions. Our review process consists of three phrases: the administrative or acceptance phase, the notification phase and scientific review, and issuance of decision phase.

The review starts when FDA receives and processes the application. After we receive it, an acceptance review is conducted to determine if the tobacco product is under FDA's jurisdiction, whether the application contains all statutory and regulatory mandated items.

In this context, I would like to mention that we have issued a rule, "Refuse to Accept Procedures for Premarket Tobacco Product Submissions," which became effective on March 21st, 2017. This rule provides some threshold criteria that all premarket submissions need to meet for FDA to accept the submission for review. The purpose of this rule is to enhance

the quality of premarket submission and to improve and expedite FDA's review process.

In this light, I have listed the 10 criteria from the rule. I'm not going to read all of these 10 criteria, but I'm going to discuss a few to help you understand why we considered this to be very basic threshold criteria.

Let's look at number 2. If the application is not in English or does not include a complete English translation, this rule will allow FDA to not accept the submission. If the application is not in English, FDA cannot read or review the application and make a decision.

Number 4, if the application does not include the applicant's contact information, FDA cannot contact the applicant on issues related to review of the application.

Number 8, if the applicant does not specify the type of submission, whether it's a substantial equivalence report or an exemption from substantial equivalence or a premarket tobacco application, FDA cannot even start an appropriate review. Therefore, we are going to refuse to accept the application.

I would like to emphasize here that this rule is applicable not only for SE but for all premarket applications.

Now let's get back to the review process. After the

acceptance review is completed, if all criteria for acceptance are met, FDA issues an acknowledgment letter, which informs the applicant that FDA has accepted the application for further processing and review. If all criteria are not met, then a refuse to accept letter is issued. The issuance of refuse to accept letter concludes the review cycle. In order for FDA to start review of the product again, the applicant needs to submit a new application.

FDA has established performance goals to finalize acceptance review and issue appropriate letter within 21 days of FDA receipt of SE report, but this performance goal is applicable for regular reports of statutorily regulated products, which include cigarette, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco.

The second phase of the review process is the notification phase. Based on public health impact review, a subset of provisional reports are slated to start review each month. FDA issues a notification letter 45 calendar days prior to the start of scientific review to inform the applicant about three items:

The scientific review start date. The applicant can amend the application anytime prior to start of scientific review

start date and the predicate eligibility determination of the predicate product has started. An acknowledgement letter is not issued for regular reports because I have mentioned before the review of regular reports start immediately upon receipt of the report.

The second purpose of notification phase is to conduct predicate determination review. FDA reviews all information submitted by the applicant for the predicate product to determine whether it is an eligible predicate product for substantial equivalence pathway.

The scientific review team is also assembled at the notification phase. Based on the content of the report, FDA assigns reviewers from the following disciplines, which I have listed on my slide. The reviewers from chemistry, microbiology, engineering, toxicology, and environmental science are assigned on a regular basis. The reviewers from other disciplines are assigned on a case-by-case basis. For example, if the application contains information about consumer perception study, a social science reviewer is assigned.

The third phase of the review process is scientific review and issuance of decision. FDA performs a multidisciplinary scientific review to evaluate if the SE report contains all

information and data to support the applicant's claim for substantial equivalence.

At the end of scientific review, depending on the nature of deficiency, an appropriate letter is issued. It could be a deficiency letter or an order letter. A deficiency letter is issued when FDA identifies that specific information is needed that would be helpful in making a decision about substantial equivalence. It could be an advice information request letter, which has 60 days of response time, or it could be a preliminary finding letter for which the due date of response is 30 days.

An order letter is issued when FDA determines that the new product is substantially equivalent to the predicate product and the product is in compliance with the Act. Otherwise, a not substantially equivalent order is issued. We refer to it as SE order and NSE, respectively.

FDA has established a performance goal to review and act on an original SE report or a resubmission within 90 days of FDA's receipt. Like before, this performance goal is for regular reports of statutorily regulated products.

During the review of an application, an applicant can withdraw their report at any time. FDA issues a letter

acknowledging the withdrawal, and that concludes the review cycle no matter what phase of the review the application is in. A provisional product cannot be legally marketed if the applicant withdraws the application before FDA completes its review and take a final decision.

For each premarket pathway, there is a specific statutory standard. The purpose of FDA's review is to determine if the application contains data and information to meet the requirements of statutory standard appropriate for that pathway.

For a determination of substantial equivalence, the applicant must demonstrate that the new product has same characteristics as the predicate product, or the new product has different characteristics than the predicate product but the differences in characteristics do not cause the new product to raise different questions of public health. This means that the new products introduced to the market through substantial equivalence pathway will not be more harmful than an eligible predicate product.

Now I'm going to discuss a couple of examples from our review to demonstrate how FDA has applied the statutory standard of substantial equivalence in its review. The first

application is for a roll-your-own paper for which we issued a substantial equivalence order.

We identified that the dimension of the new product is smaller than the dimension of the predicate product. If the dimension is smaller, the user will fill it up with less tobacco and take fewer puffs, which will in turn generate lower harmful and potentially harmful constituents, or HPHCs, if identical tobacco blend is used.

We also determined that there was some difference in the quantity of two ingredients. We do not expect the increase in quantity would significantly affect the HPHC quantity as compared to the predicate product. So at the end, we concluded the new product is substantially equivalent to the predicate product.

However, during the course of review, we also identified new products to be not substantially equivalent to the predicate product. And in the slide, I have listed a couple of examples from different applications. The first one is about predicate eligibility. A predicate is essential to the determination of substantial equivalence because we compared the new product with the predicate product. Unless we have an eligible predicate product, we do not have any reference to

compare the new product with, and we do not have a basis for issuing an order that the new product is substantially equivalent.

In addition to predicate ineligibility, significant differences in characteristics between the new and predicate products have been the reasons for issuance of NSE order. For example, in one application, the new product was not ventilated, and it was compared to a predicate product that was ventilated. The purpose of ventilation is to dilute the smoke with air. Without ventilation, smokers of the new product may be exposed to higher levels of HPHCs than smokers of the predicate product.

Although the applicant states that the changes in other parameters compensate for the lack of filter ventilation, no evidence was provided to show that is the case. So we issued an NSE order for this case.

The composition of the blend determines the HPHCs. For example, an increase in fire-cured tobacco compared to air-cured tobacco in a tobacco blend results in higher yield of BaP in tobacco smoke. In contrast, an increase in the quantity of air-cured tobacco in the tobacco blend would increase the yield of tobacco-specific nitrosamines in the tobacco smoke. A

significant difference in composition of the blend of the new and predicate products has been a reason for an NSE finding.

So here's a summary of what I have discussed today. Substantial equivalence is an alternative pathway to premarket tobacco application. The new product is compared to the predicate product for determination of substantial equivalence. The regular products cannot be legally marketed without a substantial equivalence order. The provisional products can remain on the market unless FDA issues an NSE order.

For regular reports of statutorily regulated products, FDA has established performance measures to review and act on an original SE report or a resubmission within 90 days of FDA's receipt. As Dr. Holman mentioned, it is the applicant's responsibility to provide data and information to support their claim for substantial equivalence.

In general, the TPSAC is not involved in review of the SE reports.

Thank you very much for your attention.

DR. HUANG: Thank you, Dr. Poddar.

Are there any questions? Dr. Giovino?

DR. GIOVINO: Thank you, Dr. Poddar. What would it take or what is an example of when TPSAC might get involved

with an SE process?

DR. PODDAR: I will defer this question to Dr. Holman.

DR. HOLMAN: The short answer is I don't know. You know, we've evaluated many SE reports to date, and we haven't felt inclined at this point to bring it to TPSAC. That being said, you know, there may be scenarios that come up that we haven't seen to date where we think it would be of great value and benefit to us in helping the evaluation, but I just don't know off the top of my head what that scenario would look like.

DR. GIOVINO: Okay. Thank you.

DR. HUANG: Yes. Dr. McKinney?

DR. McKINNEY: First, I want to thank you for that very comprehensive overview. It's always nice. But more importantly, I want to thank you for the examples that you gave. They provide tremendous insight.

If I may, I'd just like to ask two questions about a couple of slides. I noticed the term "significant" was used in reference to differences, and I was wondering was that a statistically significant difference when I saw that term?

In addition to that, I saw a term "expected," and I was wondering if you use modeling of some type to determine what's expected.

DR. PODDAR: Um-hum. I will defer these questions to Dr. Holman as well.

DR. HOLMAN: So significant, let me just say that it often is statistically significant but not always. We look at the totality of differences between the new and predicate product. And so there are some scenarios where looking at an individual characteristic, that difference may look relatively small, but when we put it in the context of all the differences of characteristics, it becomes significant. And so there's no absolute threshold that we use to determine what significant is. It's a compilation, again, of all the differences in characteristics.

And for the expected, can you give me the context? Can we go back to -- I'm not sure what context you're referring to.

DR. McKINNEY: It was used in question 20 in the examples, where the slight difference in blend or paper material and the expected results, etc.

DR. HOLMAN: So that's based on what data we have to date around a given issue. And so, again, looking at the difference in characteristic, if there are published studies, for example, that show that kind of difference might lead to increased exposure to toxicants, difference in use patterns, something

along those lines, then, you know, that's what we mean by expected, meaning we have some scientific information that leads us to believe that might have a detrimental effect on public health.

DR. McKINNEY: Thank you.

DR. HUANG: Yes, Dr. Weitzman?

DR. WEITZMAN: I have two questions. They relate to the same thing. You say that you accept applications if they pertain to tobacco products. How about the new nicotine delivery systems that don't necessarily contain tobacco, electronic nicotine delivery systems? And alternatively, water pipes and hookahs often contain vegetative matter that's combusted and inhaled but doesn't always contain nicotine, which I think is intrinsic to the definition of tobacco. Did that make -- did those make sense?

DR. PODDAR: Um-hum. So according to the definition of a tobacco product, a tobacco is a product that contains -- that is made or derived from tobacco, but it also includes the components and parts and accessories of a tobacco product, that they're intended to be used in combination with those products. So, in that case, even though the product does not contain nicotine or any tobacco-derived items, the components are parts

of a tobacco product or accessories.

So the new deeming regulation gave us authority to regulate the electronic nicotine delivery systems as well, so if those fit into the definition of tobacco product --

DR. WEITZMAN: Right.

DR. PODDAR: -- it comes under CTP's jurisdiction.

DR. WEITZMAN: And shisha, that doesn't come from tobacco?

DR. PODDAR: Yeah, shisha comes under our jurisdiction too, under the new deeming regulation.

DR. WEITZMAN: Thank you.

DR. PODDAR: I think Dr. Ashley would --

DR. ASHLEY: Just to clarify, shisha would -- if it's made or derived from tobacco. So that is really the definition of what is a tobacco product.

DR. WEITZMAN: Right.

DR. ASHLEY: And as Dr. Poddar said, or the components or parts that would be used. So, for example, a water pipe, the glass and the metal is not made or derived from tobacco, but it's a component or part of the use of tobacco material, so the pipe itself falls under that. Now you're talking about shisha, which does not contain tobacco, and that's still an issue we're discussing.

DR. HUANG: Dr. Ossip?

DR. OSSIP: Thank you for this excellent presentation. This is, I think, a clarification question. The presentation was very useful in terms of identifying the backdrop, the background of what is occurring in terms of SE review concurrent with the kinds of reviews that we may be doing here and what's happened historically. It was also helpful in identifying what's not in our lane to review.

What I wanted to clarify is, I believe, that given the overlap in the process -- or the content of how a particular tobacco product would be reviewed is more robust than the SE review and the comparison to predicate products but extends across reviews of multiple products through multiple mechanisms that we might be looking at here, PMTAs and so forth.

I believe that this was also educational to us in terms of giving us a more extensive background on what kinds of things the Committee would look at that we might also be looking at for the kinds of reviews that are in our lane. And I wanted to clarify that that was correct, the product characteristics, the questions that are being asked about the products separate from those related to whether, how it compares to a predicate, the population impact, characteristics, and so forth.

DR. PODDAR: I will attempt to answer your question, and then I'll defer to Dr. Holman and Dr. Ashley.

I believe, as I mentioned, that for each premarket pathway, there is specific statutory standard. So the standard that is used for substantial equivalence is different from the standard that is used for premarket tobacco application or exemption from substantial equivalence. And based on the standard, the review process and the review is determined.

Did I answer your question? Or I will let Dr. Holman and Dr. Ashley answer.

DR. OSSIP: I think I was asking less about the standards that are used for comparison to predicate products, but rather the kinds of things that you're looking at, the kind of scientific questions that you're looking for, so how it affects -- what affects risk, what might affect population --

DR. PODDAR: For substantial equivalence, we compare if the new product has the same characteristics as the predicate product or it has the different characteristics than the predicate product; if the characteristics are different, then if the differences raise different questions of public health.

So, for example, the example that I gave for design features, if one product is ventilated and the predicate -- the

new product is ventilated and the predicate product is not ventilated, in this case we determined that this difference in design feature may raise different questions of public health.

And I have also mentioned that the purpose of substantial equivalence pathway is to make sure that the new products that are introduced through substantial equivalence pathway are no more harmful than the predicate product. So this standard is different from the standard that is applied for premarket tobacco applications, where the product stands alone, and it is looked at from other aspects as well, on its impact on public health.

DR. ASHLEY: Yeah, let me --

DR. PODDAR: And I will let Dr. Ashley --

DR. ASHLEY: Let me kind of join in. But what Dr. Poddar said is exactly right. There are different standards, but generally, the issues that go in are the same. It's still a public health, population --

DR. OSSIP: That's what I'm asking.

DR. ASHLEY: -- health collection. So we're concerned around initiation in PMTA and MRTP. We're also concerned around initiation in SE because if those changes in the characteristics change initiation, change cessation, that is a

public health issue that raised different questions of public health. So it all goes in together, but the standard is a little bit different.

DR. OSSIP: Yes.

DR. ASHLEY: So, again, as Dr. Poddar just said, if it is a PMTA, then it is appropriate for protection of public health, which we consider to be this is going to improve public health. With substantial equivalence, it's really does this make it worse or not. If it's just equivalent, then that meets that standard. So it's the same issues, but --

DR. OSSIP: Yes.

DR. ASHLEY: -- it's a different standard.

DR. OSSIP: That's what I was asking about. The standards may differ, but the issues, there's a fair bit of overlap in the issues --

DR. ASHLEY: Yeah.

DR. OSSIP: Thank you.

DR. HUANG: Dr. Campopiano?

DR. CAMPOPIANO: Thank you for your presentation, and Dr. Holman as well. I feel like I understand a lot better how -- what the decision-making process are, what the building blocks are for the decisions to market a product. But I'm

struggling to form a question for something that feels a little missing.

The decision-making process seems to be driven by the product, the product characteristics, comparison to predicate products, etc., etc. And I don't see where the state of the public health can inform a recommendation or a decision, so where the -- it's all driven by product characteristics.

So, for example, if say there's a significant decrease in life expectancy, so there's an indication that population health is poorer today than it was 2 years ago, is there a process by which FDA can take the state of the public's health into consideration in making a decision to market a product that has inherent risk?

DR. HOLMAN: Under the PMTA and MRTPA pathways, that definitely is a big piece of our evaluation. Under the SE, so it's a little bit more challenging to do just that because the statute is very clear. It is just a comparison of the new to the predicate, so it's, you know, a product-to-product comparison. And so we do look at, obviously, population-level endpoints like cessation, use rates, use patterns, you know, things like that, but it's more -- certainly, under SE it's more narrowly scoped, and the overall state of the population

health has minimal bearing on those decisions.

Did I understand your question correctly in -- okay.

DR. HUANG: Dr. Weitzman?

DR. WEITZMAN: Again, we've used the term "population health" and "public health." Do I understand that correctly, that the purview of this Committee is effects on those who use these agents rather than individuals who are exposed who aren't using them? In other words, secondhand exposure, is that in any way a part of the evaluation?

DR. PODDAR: For premarket tobacco application, we look for the impact of the product on the users and nonusers of tobacco products.

DR. HOLMAN: And just to expand, I mean, we look at all populations. We look at former users, never users, current users. I mean, we evaluate the entire population in the context. And so, again, our expectation for TPSAC is, as you're evaluating MRTPAs and PMTAs, you would do the same. So issues like secondhand smoke are important in the evaluation of a new tobacco product.

DR. WEITZMAN: Thank you.

DR. HUANG: Dr. Thrasher?

DR. THRASHER: Thanks. So it also seems that the

consideration of initiation is a little harder to address in SE, particularly marketing materials or labeling that may promote use amongst youth. So how do you determine whether that is a piece of determining whether a product is substantially equivalent or not?

DR. HOLMAN: So you are correct. We don't look at labeling or advertising in the SE pathway. But we do look at product characteristics. So issues like flavor, what is the flavor of the new product compared to the predicate product. And so, you know, that's one characteristic that we look at in regards to initiation. So there are ways to look at it, but you are correct that it is more limited as to what we evaluate in making those assessments under SE, certainly much more narrow than PMTA or MRTPA.

DR. HUANG: Great. Oh, Dr. Giovino?

DR. GIOVINO: I'm just curious. In all of your reviews of the SE to date, have you ever noticed any changes in the products that weren't reported in the report?

DR. HOLMAN: Well, I mean, yeah, I'm not sure of your question.

DR. GIOVINO: Yeah, actually, have you ever noticed any characteristics of the product being considered that came to

light that were based on your investigations and that weren't reported in the company's report to you? No?

DR. HOLMAN: No. Yeah, I would say no.

DR. GIOVINO: Okay.

DR. HOLMAN: Nothing I can think of.

DR. GIOVINO: Thank you.

DR. HUANG: Okay. Any other questions?

(No response.)

DR. HUANG: Great. Thank you, Dr. Poddar.

DR. PODDAR: Thank you.

DR. HUANG: All right. We're actually a little ahead of schedule, but that was a good discussion.

So we are now scheduled to take a 15-minute break. Ask Committee members to please remember there must be no discussion of the meeting topic either amongst yourselves, with the press, or with any member of the audience.

So thank you, and we will reconvene again in this room in 15 minutes.

(Off the record at 9:49 a.m.)

(On the record at 10:05 a.m.)

DR. HUANG: Okay. We'll get back going again. So next we'll be hearing from Stephanie Redus with talking on the PMTA

and MRTPA review process.

MS. REDUS: Thank you and good morning. My name is Stephanie Redus. I am a senior regulatory health project manager in the Office of Science for the Center of Tobacco Products.

We're going to talk about the premarket tobacco application review process and the modified risk tobacco application review process.

The information in these materials is not a formal dissemination of information by FDA and does not represent Agency position or policy. This information is being provided to TPSAC to aid the Committee in its evaluation of the issues and questions referred to the Committee.

On the agenda, we're going to cover the premarket tobacco application, also known as PMTA. I'm going to discuss the review, the background, the review process, and some metrics. Then we're going to discuss the modified risk tobacco product application process, also known as the MRTPA. I'll give you some background, some key features of an MRTPA. We'll discuss the review process and provide some metrics.

So we'll start off with the PMTA. A little bit of background about a PMTA: An order is required for a new

tobacco product to be introduced and legally marketed in the United States under the Federal Food, Drug & Cosmetic Act, also known as the FD&C Act, which I will be referring to, under Section 910(a)(2).

The PMTA pathway is your primary pathway for authorization of a new tobacco product. The other alternative pathways is the substantial equivalence pathway, which Dr. Poddar spoke to, and the exemption from SE.

Now, PMTA does not require comparison to a predicate product like SE does. The PMTA can compare to the entire marketplace.

And finally, under Section 910(c)(1) of the FD&C Act, FDA intends to act on an PMT application with 180 days.

So what is a new tobacco product? It's any product that is introduced into the U.S. market after February 15th, 2007, or any tobacco product that is modified after February 15th, 2007. In order to market these products, an applicant must receive an authorization using one of the three pathways discussed.

Now let's look at the PMTA process. It's divided into five phases. First is Phase 0, which is pre-PMTA meetings; Phase 1, acceptance; Phase 2, filing; Phase 3 has two

components -- it has a substantial scientific review component and a final action component; and finally Phase 4, postmarket reporting.

Now I'd like to note that these arrow boxes do not indicate time associated with each phase of the review.

So let's dig a little deeper. Under the PMTA, pre-phase into the pre-meetings, there are several documents just to help develop your application. For example, there is the guidance for "Meetings with Industry and Investigators on the Research and Development of Tobacco Products." This is a final guidance that was revised in July of 2016.

This guidance covers how to request a meeting with the FDA and components of a meeting request. The applicant can identify specific questions for the FDA to respond to. By meeting with the FDA early in the process, the applicant will have a better idea how to design and conduct investigations intended to support their application.

The next phase is Phase 1, which is acceptance. First, does the tobacco fall under jurisdiction under Chapter 9 of the FD&C Act? Is this a product that the FDA regulates? Does the product meet the statutory definition of what a tobacco product is? And as Dr. Poddar mentioned, a tobacco product is any

product that is made or derived from tobacco intended for human consumption, including any component, part, or accessory.

The acceptance review confirms that basic elements are included for the application to be accepted. Dr. Poddar discussed the RTA in the previous presentation.

Now, there are two results that can occur from acceptance. First, the application is accepted and acknowledged, and it moves to Phase 2, or the application is refused to accept. If the application is RTA'd, there would be no additional review, and the applicant would need to submit a new application.

So let's move on to Phase 2, filing. If the application is accepted, FDA may refer the application to the Tobacco Products Scientific Advisory Committee, TPSAC, and this could be based upon FDA's own initiative or upon request from the applicant.

Now, for example, novel products may potentially be referred. Also, I mentioned the applicant can request that their application be referred to TPSAC. However, this does not necessarily mean that the application will be referred. Also, applications are not fully referred to TPSAC until which time they have been filed.

Also, at this time, samples will be requested if they were

not requested in the acknowledgement letter. An advice information request letter will be issued to an applicant at this time to request the samples. The FDA will identify the number of samples and the location to submit those samples to. These samples can be used for testing and confirmation of data submitted to support a PMTA application.

Now let's look at some of the requirements for an application under Section 919(b)(1) of the FD&C Act.

First, an application shall contain full reports and all information which should be reasonably known for investigations, studies that show the health risks of tobacco products, for example, any studies that have been published in PubMed, or other publicly available data and research conducted or contracted by the applicant. This includes raw data.

Any information listing of components, ingredients, additives, properties, the methodology of the operation of the tobacco product: For example, if you have a co-packaged ENDS product, list all the components of the package, an ENDS device, liquid or liquids, a battery, and a charger.

Next, methods, facilities, and controls for the manufacture, processing, packaging, and installation of the new tobacco product: For example, list all the locations that

manufacturer each item identified in the package.

Any identifying reference to a tobacco product standard under Section 907, which would be applicable to any aspect of the tobacco product: For example, you would want to state, if it is a cigarette, that it does not contain a characterizing flavor other than tobacco or menthol, or if your tobacco product is a smokeless tobacco product, that currently there are no 907 requirements to comply with.

Next, samples, which I previously mentioned would be requested in either an acknowledgement letter or an advice information request letter: The applicant will need to provide the requested number of samples.

Finally, specimens of the labeling proposed for the new tobacco product: For example, please provide the actual label if possible. If a copy is all that is available, please ensure the sizing is the same, it is legible, and all sides are represented.

Now, outcomes from filing: An application could be filed, and then it would move on to Phase 3 or a refuse to file, which is an RTF. If the application is RTF'd at this time, no additional review will occur; the review will halt.

If the application moves on to Phase 3, it moves into

substantive scientific review. This is a multidisciplinary approach to determine if the new product can receive an order for marketing. Some examples of discipline reviews are chemistry, engineering, and microbiology. You will hear more about these reviews in Dr. Chen's presentation.

Also during substantive scientific review, inspections are conducted. They can include clinical, nonclinical, and manufacturing. We will prioritize all the facilities based upon FDA needs. Also during this phase, sample testing most likely will be conducted.

The second component of Phase 3 is a final action. This is where either a marketing authorization is issued or a no marketing authorization letter is issued, a denial. If a marketing authorization is issued, FDA will identify postmarketing requirements in the marketing authorization letter for the tobacco product. If a no marketing authorization or denial letter is issued, a justification will be included in the letter.

And then we move on to the final phase, Phase 4, postmarket reporting. If a marketing authorization is issued, postmarket reporting is required, and the terms will be laid out in the authorization letter. Postmarket reporting can

include annual reporting requirements, such as adverse experience, labeling, and marketing information. It is information that the applicant has already gathered.

For example, in the Swedish Match North American authorization letter, three types of reporting was identified: serious and unexpected adverse experiences, manufacturing deviations, and period reporting. Note, there are no postmarket studies required to be conducted under Phase 4 for the PMTA pathway.

An application can be withdrawn at any time. If an applicant withdraws an application, FDA will issue an acknowledgement letter notifying the applicant that the application has been withdrawn. This ends the process no matter what phase the application is in.

So now let's look at some metrics for the PMTA pathway. As of March 31st, 2017, FDA has received 382 PMTA applications. Of those, 366 have been refused to accept, 14 have been acknowledged. Of the 14 that have been acknowledged, 4 were refused to file, 8 were filed. FDA has issued eight marketing authorization letters. Please note, the numbers may not add up due to rescinded letters or to pending applications.

So there is some additional guidance that's available to

an applicant to develop their PMTA application. First is the "Applications for Premarket Review of New Tobacco Products." This draft guidance issued in September of 2001 [sic]. This guidance describes who submits a PMTA, when you should submit a PMTA, and the contents of the application. For example, full reports of investigations of health risks should be included.

The next guidance is the "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS)." This issued in May of 2016, and it is a draft guidance. This guidance contains information specific to supporting an application for a PMTA for an ENDS product. It contains definitions for accessories, components, or parts, and terminology used when discussing ENDS products. It covers descriptive information about ENDS products and provides examples of information that an applicant may need to submit depending upon the product.

The next guidance is the "Tobacco Product Master Files." This was a final guidance that issued in May of 2016. This discusses who are authorized to use a TPMF, a tobacco product master file, who's authorized, and how a TPMF works.

The final guidance listed is the "National Environmental Policy Act; Environmental Assessments for Tobacco Products;

Categorical Exclusions" for small entity guidance. This is a final guidance that issued in October of 2015, and this is in addition to the National Environmental Policy Act rule that issued.

So now let's move over to the modified risk tobacco application pathway. A little bit of background for MRTPAs: Modified risk tobacco products are tobacco products sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. This includes products' labels, labeling, or advertising, and this material explicitly or implicitly indicates that the product is less harmful or presents a lower risk of tobacco-related disease than other commercially marketed tobacco products; the tobacco product or its smoke contains a reduced level of, or presents reduced exposure to, or does not contain/is free of a substance.

In order to market a modified risk product, the applicant must receive a modified risk order in order to market. There are two types of orders that can be issued: a risk modification order and an exposure modification order. You will hear more about these in a future presentation from Dr. Apelberg.

Also, a tobacco product is considered a modified risk

product if there are descriptors, such as "light," "mild," "low," or similar descriptors that's utilized in the label, labeling, or advertising.

Now, in order for an MRTP product to be legally introduced or delivered for introduction into interstate commerce, an application must be filed with the FDA, and the FDA must issue an order per the FD&C Act, Section 911(g), with respect to such product, allowing it to be introduced or delivered for introduction into interstate commerce.

Now let's look at some key features for modified risk application and orders. First, the FDA must make MRTPAs, except for personal privacy, trade secrets, or otherwise confidential commercial information, available for public comment. FDA must refer MRTPAs to the TPSAC for recommendations. An application for renewal may or may not be referred to TPSAC. Also, the FDA intends to make a decision on a MRTPA within 360 days. Please note that the 360 days from the review is from the MRTPA guidance that issued in March of 2012. This is not a statutory requirement.

A decision is a modified risk order, a denial, or a response letter, which I will cover more later on in the presentation. MRTP orders are issued for individual products,

not for a class of products. For example, another applicant cannot piggyback on an order issued, meaning that the applicant can only utilize their own orders. They are also issued for a specified time. An applicant may request renewal of their order for a product.

Now let's look at the review process. As you will note, this process looks very similar to the PMTA process that I covered earlier. There are, again, five phases. First is Phase 0, pre-MRTPA meetings; Phase 1, acceptance; Phase 2 for filing; Phase 3, two components, review and final action; and Phase 4, postmarket surveillance and studies. Note, there is the renewal process identified here in this particular presentation.

Now I'm going to cover the differences between the two pathways. First, under the filing phase, for filing of a modified risk tobacco product, the following items are necessary:

A description of the proposed product, proposed advertising and labeling. Some examples of this information include the brand name, the sub-brand, a description of the product form. For example, is it a liquid, a gel, a strip, or a stick?

Next, the conditions for using the product: for example, full description on how a consumer will use the product, how to operate the product, if the product is designed to be inhaled, smoked, sniffed, or chewed, the length of time for a consumer to consume a single unit of product, and the pattern of usage.

Next, the formulation for the proposed tobacco product: a complete list of uniquely identified components, ingredients, and additives by quantity, including specifications and intended function of each item; a description of tobacco blending, reconstitution, and manipulation; also, any stability data for the stated shelf-life.

Next, sample tobacco products of the labels and labeling: copies of the products' labels and labeling, including each variation proposed, including inserts and onserts.

Next, all documents relating to the research findings that are conducted relating to the effect of the product on related diseases and health-related conditions: This includes favorable and unfavorable information about the product's ability to reduce risk and exposure and relating to human health. This includes all public available information per the statute. This includes study reports and raw data. If any of the information is not available, the applicant should provide

an explanation for the omission.

Now, data and information on how individuals actually use the tobacco product: This is data generated from the consumer from both use and controlled environments and in a natural environment.

And finally, any such information identified by the Secretary. Some examples of this could be additional product analysis, data to support comparative claims, or products that have been on the market prior to the MRTPA application. FDA will identify and notify the applicant of this required information.

Another difference is under substantive scientific review. It's still a multidisciplinary approach. We still conduct inspections under clinical/nonclinical and manufacturing. But this is where TPSAC comes in as a publicly -- TPSAC publicly provides recommendations to the FDA.

For example, each TPSAC meeting has a particular focus. The last meeting for the Swedish Match, the FDA had focus questions for the Committee to review from the application. For example, a question that was identified was how would you recommend that the FDA evaluate the relative health risks to individuals of the MRTP. Please refer to the documents that's

located on the CTP website for additional information from the TPSAC meeting.

Now, another difference is the decisions that may result. There are three options: First is a modified risk order, MRO; a denial; or a response letter. A response letter is not an outright denial. FDA believes that the claim has merits and is willing to work with an applicant with the application.

For example, the response letter to Swedish Match included two time frames. The first was within 45 days of receiving the letter, the applicant should request a meeting and notify the Agency of its intent to amend or withdraw the application.

FDA requests that the applicant either amend or withdraw the application within 24 months. Applicants are encouraged to meet with the Agency to discuss the steps necessary for issuance of modified risk orders.

Note, an applicant could receive more than one type of decision. For example, Swedish Match submitted multiple claims. They received a denial letter and a response letter for multiple claims. These are also available on the CTP website.

Phase 4 difference: postmarket surveillance and studies. Under Phase 4 for an MRTPA, studies are required. The

postmarket surveillance and study activities include an applicant should submit a postmarket surveillance protocol to FDA; FDA reviews the proposed protocol, determines whether to approve it; then the FDA will monitor and reviews data submitted as part of postmarket surveillance.

Now let's recap. In order for an MRTPA to be legally introduced or delivered for introduction into interstate commerce, an MRTP application must be filed with FDA. And an order under Section 911(g) with respect to such product allowing it to be introduced or delivered for introduction into interstate commerce must be in effect. And an applicant must also satisfy any applicable premarket requirements under Section 910 of the FD&C Act. If an MRTP is a new tobacco product, it must be brought to market through one of the following pathways: the PMTA; substantial equivalence, SE; or exemption from SE.

Now let's look at some of the metrics for the PMTA program. To date, as of March 31st, 2017, FDA has received 36 MRTPAs. Of those 36, 10 were refuse to accept, 19 were acknowledged and moved to filing. Of those that were filed, 4 were refused to file, 10 were filed. Now, eight denial letters have been issued, and eight response letters have been issued.

And five applications have been withdrawn. Again, please note that these numbers may not add up due to pending applications.

In addition, there are some additional guidances that's available to an applicant in preparation of their application. The first is the draft guidance that issued in April of 2012. It is the "Modified Risk Tobacco Product Applications Guidance." This guidance describes a modified risk tobacco product, the risk modification orders, and an exposure modification order. It covers who should submit an MRTPA, when an MRTPA would need to be submitted, and it also discusses the contents of an application.

The other two guidances I discussed in the PMTA process.

So the take-home points from my discussion today are FDA is committed to working with applicants early in the process. We encourage pre-meetings. An applicant then is responsible for submitting a complete application. Also, the PMTA pathway is the primary pathway for authorizing and taking a new tobacco product to market. And finally, an MRTP is an authorization to market the product as reducing the harm or risk of tobacco-related disease.

Thank you.

DR. HUANG: Great. Thank you for your presentation.

I have one question. Just if you could again describe the response versus denial?

MS. REDUS: A denial is we've determined that the supporting documentation that was provided does not support the claim that was submitted. A response letter indicates that the FDA believes that the claim has merit and is willing to work with the applicant to identify additional studies that may be able to support their claims.

DR. HUANG: Thank you.

Are there other questions? Dr. Giovino?

DR. GIOVINO: If I did my math right, 96% of the PMTAs that were received were RTA'd?

MS. REDUS: That is correct.

DR. GIOVINO: So are there any major categorical reasons? Like, you know, among those 366, what were the major reasons?

MS. REDUS: Product identification was a critical piece, and having not followed guidances thoroughly and provided all the required elements under Section 911 for premarket tobacco application.

DR. HUANG: Okay. Dr. Fagan?

DR. FAGAN: Just for clarification and to follow up on Dr. Huang's question, if a sample comes in and the FDA tests it

and the tests are different from what the applicant has submitted, is that a denial or a response?

MS. REDUS: That goes to -- a determination is -- information looked at through the entire application, and it will be looked at in the method and the matter appropriate for that. I'll turn it over to Dr. Holman to speak a little bit more about that.

DR. HOLMAN: I can't give you a definitive answer because I think it depends a lot on the specifics. There may be reasons why our analyses do not align with the applicant's analysis. And, you know, so depending on what those reasons are, you know, we may actually issue a response. And part of that response may be trying to get our analyses to align.

Now, if I think there are marked differences between our analysis and theirs, that may be more likely to lead to a denial. So, again, I think it depends on the particulars.

The whole point of the response is we think there's enough merit in what's in the application that with additional work by the applicant and additional advice from the FDA, there's a possibility that we could issue an MRO. A denial is a situation where, for whatever reason -- maybe it's analysis, maybe it's something else -- we don't think that there's a very

high likelihood that the applicant would be able to address whatever deficiencies we had identified in our evaluation.

And I want Dr. Chen to actually comment on the reason for the RTAs.

DR. CHEN: Dr. Giovino, to respond to your question, sometimes it's a jurisdictional issue, that an applicant may think that they need a PMTA for their product and it's not under our jurisdiction. And oftentimes we've found that applicants have a hard time understanding the full requirements of an environmental assessment.

And to respond to that and other questions that have arisen, FDA has provided an informational seminar to try to help applicants understand the different components, contents, and formatting of the PMTAs. So that's all publicly available information.

DR. HUANG: I have one follow-up also. What is the timeline following a response letter?

DR. HOLMAN: Stephanie talked about the timeline for the applicant to respond, which was 45 days, to let us know whether they intend, in fact, to amend their application. But other than that, there's not a strict timeline on the applicant to resubmit their amended application to us.

DR. HUANG: Okay. Thank you.

Yes?

DR. THRASHER: Jim Thrasher. So with regard to the postmarket reporting, I'm wondering the extent to which marketing materials need to be provided, new marketing materials that aren't shared in the first phase of the evaluation, that those need to be shared with FDA and evaluated in some meaningful way in terms of particularly their impact on youth or on, you know, keeping smokers from quitting.

DR. CHEN: Yes. In terms of PMTAs, I'll specifically talk about that. There are requirements that are in the authorization letter that delineate the materials that we're interested in evaluating. And there is a team of scientists that look at specific materials, so advertising, as you said, or labeling materials. And then we will look at the materials submitted as well as any studies or information that may exist to support decisions and review evaluations that we make.

And then the, you know, end decision is does it continue to be appropriate for the protection of the public health, does a product continue to be appropriate, and that's our analysis.

DR. HUANG: Dr. Ossip?

DR. OSSIP: Thank you. I have two questions follow-up on

the postmarketing. One is what role does TPSAC play in that postmarketing process? And then the second is during Phase II PMTA filing, they have FDA may refer an application to TPSAC. I wonder if you could speak a bit more about the situations in which it may or may not be referred to TPSAC?

MS. REDUS: Well, in response to whether an application may or may not, we're going to look at novel products and any uniqueness to these types of products and then additional guidance from there. I'll let Dr. Chen respond.

DR. CHEN: For PMTAs, it's not a requirement that the applications are referred to TPSAC. However, if there's any sort of scientific questions that we feel that could benefit from TPSAC's discussion, then we will then refer the application for a discussion.

For Swedish Match, which is the one example that I have, we did not refer it to TPSAC because it just had been discussed by TPSAC for the MRTPA for the same products. And we felt that the scientific questions that would arise from the PMTA were very similar to the MRTP discussions. And so we felt like there was no need to duplicate a TPSAC committee for the same products. So that's an example that occurred.

DR. APELBERG: Just to chime in on the part of the

question that was focused on TPSAC's role in the postmarket surveillance, postmarket reporting for MRTPA, you know, for the meeting that occurred 2 years ago for Swedish Match, one of the topics that we did bring to the Committee for discussion were considerations related to postmarket surveillance and studies, should an order be issued. So there, you know, may be an opportunity for TPSAC at that point in time to comment on sort of unique factors or features that I think would be important should an order be issued.

DR. HUANG: Yes, Dr. Ossip?

DR. OSSIP: May I follow up on that? So if the -- might TPSAC be involved depending on the results of the postmarketing surveillance, or is that handled through other channels?

DR. APELBERG: I think TPSAC may be involved. I think it would be dependent on, you know, on a case-by-case basis.

DR. HUANG: Yeah. Dr. Ashley?

DR. ASHLEY: Just to throw in a little bit. One of the things that Stephanie talked about but maybe not have come across as strongly as to make sure you guys understand, so MRTPs are for a certain set period of time. And so the applicant has to provide data to FDA during that time, where we can better evaluate whether what we thought was going to happen

is actually happening. And when that time is over, then the applicant can come back to FDA for a renewal.

And depending on the situation -- and I don't know that we've really decided TPSAC's role in that renewal, but I could clearly see the opportunity for TPSAC to review that data as part of that renewal process to make determinations of whether that should be renewed. So I think there will be a role of TPSAC to play in those -- in looking at some of that postmarketing data and particularly in reference to a renewal, a reapplication.

DR. HUANG: Yes. Dr. King?

DR. KING: I have two questions related to the MRTPA order. It says here that it's valid for a duration specified by FDA. And I'm wondering is there a base-level duration, or what's the -- is it going to vary by the product, or what is the actual specification for the duration that it would be applicable?

And then, in terms of the renewal, I'm wondering with regard to that process, is it an abbreviated process or is it, you know, going back from the beginning, or have you not decided yet? I'm not fully clear on the renewal process.

MS. REDUS: For the timeline for an application for an

order, if it is a G2 order, according to the statute, it is valid for 5 years. For a G1, I will let Dr. Chen and Dr. Apelberg speak to those.

DR. APELBERG: Yeah. The G2, it's in the statute, a maximum of 5 years, and G1, it would be up to FDA to make the determination of the time period for the order.

UNIDENTIFIED SPEAKER: A case-by-case?

DR. APELBERG: Yeah, no, it'd just be a case-by-case basis.

DR. ASHLEY: Kind of an answer to your question, we haven't had to deal with that yet, so it's still -- I mean, I think early on it's going to be on a case-by-case basis. We're going to see. And I'm sure part of it is our confidence that we believe that this is going to achieve what we think it's going to achieve, or our lack of confidence in that. And so, again, we haven't had to encounter that yet. And so when we start dealing with those cases, then we'll have more details.

DR. HOLMAN: And to address your question about what does the renewal look like, is it a full evaluation, sort of a de novo almost evaluation, again, we haven't been there yet. We haven't done that yet. But my expectation is that it would be certainly a more abbreviated application and evaluation in

comparison to the original application that we issued the marketing order on.

I mean, it would be focused on, you know, likely things like how has the marketplace changed over that period of time and does that have any bearing -- or what bearing does it have on the public health impact of that product because, as you know, the marketplace has been changing very rapidly over the last 5 to 10 years. And, you know, I would anticipate it will continue to evolve rapidly. And so it's really going to be more focused, I think, on that is my, you know, expectation this time.

DR. HUANG: Yes. Dr. McKinney?

DR. McKINNEY: Once again, very nice presentation. Having read the Act, I know that that information is all over the Act, and you did a nice job summarizing it. Thank you.

My question is related to slide number 11, where if we look at that, it says that the application should contain information that shows that the product in question or the subject of the PMTA has less risk than other tobacco products.

And my question is related to the role of the TPSAC in reviewing information. As I reviewed the information that was provided from Swedish Match, the information provided for us to

review for this meeting, there was a focus on tooth decay. But there was not much conversation about that product causing less tooth decay than, say, other tobacco products, maybe even comparing it to cigarettes.

Is that something that the Committee should always think about when they're reviewing these applications, the comparison or relative risk?

DR. CHEN: I want to clarify that the discussion that took place was concerning the MRTPAs, so not the PMTAs. And so there was a different discussion and focus, and that would be one thing.

And so, but thinking about PMTAs, I think that it talks about comparative risk, and I think that it should be a broad comparison in general that the Committee would think about. And again, in order for something to be appropriate for the protection of public health, what does that entail?

And so I think that, you know, for the snus products, there was a discussion on oral disease in general. And so there was discussion about tooth decay and gum disease as well as oral cancers, and that had to do with the claims that were being presented for the MRTPA purpose. So I think there was a different focus, again, because of the claims that were being

presented.

DR. HUANG: Yes, Dr. McKinney?

DR. McKINNEY: One more follow-up question. And you mentioned that there were no questions, or the PMTA was not -- well, that TPSAC was not asked to review the PMTA because of the discussions that occurred with the MRTP. And I'm just a little bit confused about the standard and how the MRTP discussion was applied to the PMTA, which TPSAC did not review?

DR. CHEN: I think that, broadly speaking, there was an agreement by the TPSAC committee that there were less overall oral cancer, for example, prevalence of oral cancer for users of Swedish Match snus, for example, compared to other U.S. smokeless tobacco products. And so I think, broadly speaking, that, you know, when you looked at Swedish Match snus products, that compared to the U.S. smokeless tobacco products, again, for certain disease areas, there was less risk.

And so it was kind of the Swedish Match snus products to the general U.S. smokeless tobacco product market. And so in that comparison, that there wasn't any sort of additional discussion that we felt was necessary for the PMTAs.

And it's not just one disease that we're looking at, right? We're looking at use patterns, initiation, cessation,

poly-use, as well as individual disease risk. So when we're looking at PMTAs, we're looking at a whole gamut of information and not just focusing necessarily on one issue, and whereas MRTPAs, you're looking at a particular claim, so you're specifically looking at specific disease risks pertinent to the claim that's being discussed. So there is a little difference.

DR. APELBERG: Yeah, and just to add to that, I mean, your initial comment about the gum disease and tooth loss -- and this is something I'll go into in my presentation -- you know, for an MRTP, the application is for the product to be marketed with specific modified risk information. So the information that FDA is evaluating in the decision that we're making is based on what the request is from the company. That's also the basis for what we're going to be bringing to TPSAC.

So in that case, there wasn't a claim by the company that gum disease and tooth loss -- you know, that there was a lower risk of gum disease and tooth loss in, you know, their products compared to some other products. It was to remove a warning, you know, and therefore an implied claim that there's no risk of gum disease and tooth loss. So it's dependent on the specific claims and the specific types of modified risk information.

And again, I'll just add to what Ii-Lun said about the relevance to PMTA. You know, one of the main parts of the discussion was about the relative risk compared to cigarettes, as well, because that was also one of the claims. So, obviously, there was a lot of discussion and information there that could be used to inform, you know, the overall PMTA review.

DR. HUANG: Yes, Dr. Wanke?

DR. WANKE: Just a quick question. So as part of the PMTA and the MRTPA processes, it includes a submission of the product for FDA to evaluate or examine. Is that also part of the process for the SE, for substantial equivalence, sample submission?

DR. HOLMAN: No, we do not get any samples under the SE pathway.

DR. WANKE: Okay.

DR. HUANG: No other questions?

(No response.)

DR. HUANG: Great. Thank you very much.

MS. REDUS: Thank you.

DR. HUANG: Okay. Now it's time for our Open Public Hearing.

And so both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee place great importance in the Open Public Hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this Open Public Hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair.

Thank you for your cooperation.

So let's see. First speaker is Dr. Ogden?

DR. OGDEN: Mr. Chairman, ladies and gentlemen, good morning. Thank you for the opportunity to speak today about a very important issue, and that's FDA's premarket review of tobacco products.

I'm Mike Ogden, Vice President of Scientific and Regulatory Affairs for RAI Services Company. And I'm here on behalf of Reynolds American operating companies, including R.J. Reynolds Tobacco Company, American Snuff Company, Santa Fe Natural Tobacco Company, Kentucky BioProcessing, Incorporated, and R.J. Reynolds Vapor Company.

In the *Federal Register* notice announcing this meeting, FDA stated that the purpose of the meeting was to discuss FDA's premarket review of tobacco products, including PMTAs, SE, and MRTPAs. While FDA's briefing package, and indeed the

introductory comments made this morning, indicates a focus on PMTA and MRTPA, I would like to focus on substantial equivalence, or SE, pathways.

Substantial equivalence is especially important to discuss today as this is the premarket review pathway with which FDA has had the most experience in the almost 8 years since the enactment of the Tobacco Control Act. And FDA has not adequately implemented this pathway. Rather, the industry lacks sufficient guidance to successfully use the SE exemption and SE premarket review pathway, and these paths are, as currently interpreted by FDA, are impractical and unworkable.

It is important that FDA resolve the issues with these pathways and faithfully implement the Tobacco Control Act consistent with Congress's intent. This can only help FDA's review of PMTA and MRTPAs.

As you know, the Tobacco Control Act provides three regulatory pathways by which manufacturers may obtain authorization to market new tobacco products. First, by seeking an exemption for products that include only minor modifications to tobacco additives; or second, by demonstrating that the new product is substantially equivalent to a predicate product; or third, by filing an extensive premarket tobacco

application with detailed evidentiary support.

Congress intended these premarket review pathways to differ in the level of regulatory oversight. Indeed, Congress designed the statute to allow new products to enter the market in a timely manner through different review pathways that reflect the different level of regulatory oversight.

Congress intended minor modifications to be exempt from SE review altogether, and SE reports, when warranted, then to require less supporting data and information and therefore result in a faster and less burdensome review pathway than premarket tobacco product applications. Indeed, the SE exemption request pathway should be the least onerous, least burdensome pathway for manufacturers to make minor modifications to their tobacco products, but it is not.

To underscore this point, FDA has cleared one SE exemption request in the nearly 6 years since the SE exemption request regulation was promulgated, all while refusing to accept 55 applications. The confusion due to the lack of functional regulation and guidance regarding the current SE exemption request effectively nullifies the use of the exemption pathway.

FDA needs to clarify through regulation that when changes between a new and predicate product involve changes to the

ingredient composition of the products, the SE exemption pathway should be used. These types of changes include a change in the type or level of flavors, the type or level of filter or paper components, or combinations of the above.

Once FDA clarifies the SE exemption pathway, the focus then shifts to those changes that fit within the SE pathway. Under the Tobacco Control Act, FDA is required to issue an order finding substantial equivalence if the new tobacco product has the same characteristics as a predicate product and/or if the new product has different characteristics but those different characteristics do not cause the product to raise different questions of public health.

This statutory scheme, which mirrors that of the medical device regime established in 1976, required two different pathways for FDA to find substantial equivalence. However, FDA has not adequately implemented the statute's substantial equivalence pathway. Rather, FDA has incorrectly interpreted the statutory phrase "same characteristics" to mean "identical" physical characteristics to the predicate product in all respects. Thus, under this interpretation, every change, no matter how slight, incorrectly places the new tobacco product under the second prong of the SE pathway.

FDA has placed undue and unreasonable importance on every individual change to a specific ingredient, material, or characteristic, no matter how minor or unrelated to public health and without offering any explanation why these individual differences in characteristics could even possibly implicate different questions of public health.

However, "same" cannot mean "identical." We know that FDA's current interpretation of the SE pathway was explicitly rejected by the District Court for the District of Columbia in August 2016, which found that the statutory exemption for "minor modifications cannot be squared with same characteristics as meaning identical characteristics. Congress plainly meant to exclude from a substantial equivalence showing some new products that, although possessing different physical characteristics than their predicate, did not raise sufficient health risks to warrant an FDA review."

Indeed, the Court found that "it is not reasonable to think that Congress intended to channel all non-exempt physical modifications through the different characteristic prong. If it had wanted such a result, it would have said so expressly and not allow for SE exemptions. However, it created a less burdensome same characteristic prong that seemingly was

intended for physical changes that were more than minor but yet not so significant as to require a showing through clinical data, if demanded, that the product does not raise different questions of public health."

The level of change reviewed under the same characteristics prong must exceed the level of change reviewed under the SE exemption pathway so as to give meaning to congressional intent. And the different characteristics prong must exceed the level of change reviewed under the same characteristics prong.

In keeping with the SE framework developed for medical devices and on which Congress modeled the tobacco product regime, FDA must borrow from the core SE principles established in the device context in interpreting the parameters of the term "substantially equivalent" with regard to tobacco products.

FDA must interpret the same characteristics prong of the SE pathway to be less burdensome than the different characteristics prong. The same characteristics prong should apply to products in which the new product differs from the predicate in one or more design characteristics but the types of components used to construct the new product and the

predicate and the intended use to which the new product and the predicate operate are the same.

For example, the same characteristics prong should be used to evaluate a new cigarette product like the predicate that incorporates a filter, tipping paper, and cigarette paper but differs perhaps in ventilation and filter efficiency.

Under the second prong in those limited circumstances when a product does contain a materially different characteristic, FDA must determine the product is substantially equivalent if the chemistry demonstrates that the new product, when viewed in its entirety, does not raise different questions of public health or when FDA cannot conclude that the differences scientifically demonstrate that the new product will substantially increase the risk of tobacco-related diseases. As discussed in the August 2016 D.C. court ruling, these differences may be fairly significant.

We believe FDA should promulgate regulations that, at a minimum, establish content and format requirements for SE reports. They should establish consistent review procedures and clearly inform regulated industry as to what those procedures are, identify the characteristics that are relevant to SE reports, and establish regulatory interpretation of the

same characteristics and different characteristics prongs of the statute; and finally, should establish a scientifically based regulatory standard for determining when a tobacco product presents different questions of public health.

Thank you.

DR. HUANG: Thank you.

Our next public hearing speaker is Dr. Murillo.

MR. MURILLO: Thank you, Mr. Chairman, members of the Committee, and ladies and gentlemen. I appreciate the opportunity to address this Committee.

My name is Joe Murillo. I am Vice President of Regulatory Affairs for Altria Client Services. I'm here today on behalf of the Altria family of companies, which manufacture and sell cigarettes, smokeless tobacco, cigars, e-vapor, and other tobacco products.

The Family Smoking Prevention and Tobacco Control Act provided FDA new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products. It has been nearly 8 years since Congress passed the FSPTCA empowering FDA to regulate certain tobacco products, and we have all learned a lot during these years.

Last year, FDA expanded its oversight to now regulate other tobacco products, including cigars and e-vapor products. Today, as FDA's meeting notice requested, I would like to provide the Committee our perspective on the statutory and scientific standards applicable to tobacco products' applications, including substantial equivalence, premarket tobacco, and modified risk tobacco product applications.

The TPSAC has an important role to play in providing advice, information, and recommendations to the FDA on a number of topics and products, including those products that may potentially reduce risk for all tobacco product consumers. To that end, we encourage the Committee to carefully evaluate scientific information on the relative risk of different tobacco products and to provide perspective to the Agency in a way that supports tobacco product innovation and tobacco harm reduction.

Importantly, authorizing potentially less risky tobacco products and providing clear, accurate, and scientifically grounded communications about those products to adult tobacco consumers are among the most significant opportunities for the FDA and indeed for all of us to advance tobacco harm reduction.

The Act establishes several pathways for FDA to authorize

the introduction of new products into interstate commerce. Section 905 of the Act defines substantial equivalence or substantially equivalent to mean that a new product has (1) the same characteristics as a predicate tobacco product, or (2) has different characteristics, but the product does not raise different questions of public health.

In other words, FDA must issue an order for substantial equivalence if the new product has the same characteristics as a predicate product, or FDA should issue an order finding substantial equivalence if the information an applicant submits demonstrates that the product, while having different characteristics, does not raise different questions of public health.

Congress intended for the substantial equivalence pathway to be faster and less burdensome than other forms of premarket review, such as PMTAs. Substantial equivalence was intended for companies to be able to make incremental changes to marketed products so long as a new product satisfied the same characteristics prongs or the no different questions of public health prong of the pathway.

Turning to premarket tobacco applications, Section 910 of the Act provides for premarket review of new tobacco products

in instances where a manufacturer does not pursue the substantial equivalence pathway. The Agency must find that the authorization to market such products is appropriate for the protection of public health, including with respect to users and nonusers of tobacco products.

The diversity of potential new tobacco products requires diverse applicant approaches to testing and analyzing scientific information in support of a PMTA. The Agency should base its evaluation of whether a new tobacco product is appropriate for the protection of public health on an integrated risk/benefit analysis, not a single health outcome.

Benefits result from anticipated reductions in morbidity and mortality from a new tobacco product's use relative to more risky forms of tobacco. The Agency should weigh these benefits against potential risks resulting from a product's introduction, such as increased initiation or decreased cessation.

We have previously expressed our concerns with certain FDA proposals to establish considerable evidentiary requirements for PMTA applicants, such as those established in the recent ENDS guidance. Further, we have urged FDA to establish product pathways that reflect reasonable regulation, comply with the

statutory requirements set by Congress, conform with Congress's intent, and support manufacturers' efforts to develop and bring to market innovative products that may advance the public health. An unduly burdensome PMTA process will effectively preclude the introduction of new tobacco products that may reduce risks and stifle innovation.

Turning to modified risk tobacco product applications, under the FSPTCA, Congress sought to protect and promote public health by empowering FDA to address the risk and harm associated with current tobacco use. In creating Section 911, Congress recognized the contribution that modified risk tobacco products and informing consumers about such products could make in achieving this important public health goal.

Harm reduction through migration of adult smokers to lower-risk tobacco products could reduce the prevalence and severity of disease from cigarette smoking for those who do not cease tobacco product use. In this context, introduction of reduced-risk tobacco products into the marketplace, including those with MRTP claims, is critical.

The Act establishes five areas of investigation that an applicant must address in support of an MRTP application. First, the individual health risks of the product; second, the

likely effect of the MRTP on tobacco cessation in current users; third, the likely effect of the MRTP on initiation in nonusers; fourth, the risks and benefits of the MRTP compared to cessation products; and finally, comprehension of the MRTP's advertising and labeling.

Scientific standards for evaluating MRTPs must be rigorous. These standards, however, cannot be so rigorous that they prevent applicants from marketing MRTPs. We continue to urge the Agency to accept flexible approaches to providing scientific evidence in support of such applications. There must be a balance to ensure that CTP can sufficiently evaluate MRTPs without unduly inhibiting their introduction into the marketplace, consistent with the statutory mandate.

If the industry is not able to take full advantage of the public health opportunity presented by consumer-acceptable lower-risk tobacco products, cigarette smoking may unintentionally be preserved as the dominant form of tobacco use in the United States.

We at Altria continue to support FDA's regulation of all tobacco products. Such regulation, however, must allow industry participants to engage and compete in a dynamic market. The combination of innovative and potentially less

harmful tobacco products and adult tobacco consumer interest in such products presents FDA with an unprecedented opportunity to help reduce the harms associated with tobacco use, thereby advancing public health.

We encourage this Committee to give careful and thoughtful consideration to these issues in providing any advice or recommendations to the Agency on premarket or modified risk tobacco product applications; for that matter, potential product standards or any other scientific issues that may be coming before this group. Further, we urge the Committee to take into account the importance of providing adult tobacco consumers truthful and accurate information about the potential for risk reduction presented by different tobacco products.

Thank you again for the opportunity to address you today.

DR. HUANG: Thank you for your comments.

The Open Public Hearing portion of this meeting has now concluded, and we'll no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee as well as the public comments.

Now we're ahead of schedule, and we had previously had lunch scheduled, but now I think we're going to -- since lunch

isn't even here, we're going to have Dr. Chen present now.

So if I could invite Dr. Chen?

DR. CHEN: I get to avoid the postprandial dip time, so that's good.

(Laughter.)

DR. CHEN: All right. So most people are familiar with the concept of premarket authorization of regulated products, such as drugs and devices, and with the enactment of the 2009 Tobacco Control Act, FDA now has the authority to regulate tobacco products.

As was mentioned earlier, before a new tobacco product can be legally marketed, that is, a product that was not on the market as of February 15th, 2007, a premarket tobacco application must be submitted, reviewed by the FDA, and determined to be appropriate for the protection of public health so that it may be introduced into interstate commerce unless the product is found to be substantially equivalent, SE, to a predicate tobacco product, in other words, a grandfathered tobacco product, or the product is found to be exempt from SE.

Stephanie Redus described the PMTA process with a focus on the administrative aspects. My presentation will focus on the scientific review, although there'll be a little bit of overlap

in materials presented.

Section 910(c)(2)(A) of the FD&C Act states that the FDA must determine whether permitting this product to be marketed would be appropriate for the protection of public health. So let's delve more into that.

FDA must evaluate a product's impact on current tobacco product users as well as nonusers. Non-users may be individuals who had not previously used tobacco products who experiment or initiate tobacco product use, or it may be those individuals who do not use tobacco products but are exposed to tobacco via second or thirdhand exposures.

FDA's evaluation of the available evidence on the proposed product as well as comparative tobacco products involve understanding the risks and benefits to users and nonusers, including understanding use behaviors such as likelihood of initiation of the proposed tobacco product, potential poly-use of tobacco products, and cessation of tobacco products.

Section 910(b)(1) of the Tobacco Control Act states that a PMTA must contain the bulleted items shown. This was discussed by Stephanie Redus earlier. In other words, the PMTA needs to include information on how the product is made and packages, what it is, how it is used, and health risks as well as

comparative risks to other tobacco products.

It is important for FDA to be able to understand how consumers and others are impacted by the availability of a new tobacco product within the context of currently available tobacco products.

There are some other requirements for the PMTA. Notably, labeling of the proposed product must be submitted, and if there were any product standards established, the proposed product would need to meet such product standards. Samples of proposed products may be requested for FDA testing purposes. The environmental assessment should be prepared in accordance with appropriate regulations found under 21 C.F.R. Part 25.

In September 2011, FDA published a draft PMTA guidance, and more recently, FDA published a draft guidance on PMTAs specifically for ENDS products in May of 2016 along with the publication of the deeming rule. Draft guidances are available for public comment, and when the draft guidances are finalized, they will then represent FDA's thinking on PMTAs for regulated tobacco products.

The draft guidances on PMTA state the following information is helpful to assess the nonclinical health risks information of a new tobacco product: details on what the

product is and how the product is made; a full assessment of the toxicological profile, including a thorough literature review such as probative information on health risks and addictiveness by evaluating user exposure to tobacco-related compounds; and a summary discussing how the new tobacco product would be appropriate for the protection of public health relative to similar comparator as well as to the general tobacco product market.

Back a few slides, I mentioned that the statute requires the applicants show the health risks of the tobacco product. The bulleted points here help to understand the potential impact of a new tobacco product. Also important is an understanding of whether the new tobacco product presents lower risks than other tobacco products.

An evaluation of a proposed product in comparison to the current tobacco product use environment is important. As an example, in the Swedish Match North America PMTA, the applicant compared their snus product manufacturing process to other types of smokeless products to demonstrate how their specific processes decreases toxicological risks in their products. Chemical analysis of their products were compared to chemical analysis of other smokeless tobacco products on the market.

Other comparisons discussed in the application included but were not limited to nicotine levels and nicotine pharmacokinetics, use behavior, perception, and acceptability.

Additional information useful to support a PMTA include description of label comprehension, potential misuse, and human factor issues. It is most helpful, in general, when study findings are generalizable to the population of U.S. users and nonusers of the new tobacco product.

The draft guidance on PMTAs available for comment states:

Alternatives to U.S.-conducted randomized controlled clinical trials may be appropriate when potential bias associated with alternative controls can be addressed. Literature reviews or other reports may be acceptable to support a PMTA but are generally considered less robust. Conducting independent analyses of published studies can support a PMTA. However, critical study detail should be included for FDA to review. Bridging data and studies can reduce the need for large amounts of additional data submitted.

On November 10th, 2015, FDA issued the first marketing orders allowing eight Swedish Match North America snus products to be introduced into interstate commerce via the PMTA pathway. We will now take a look at that review and decision process as

an example of an application that could potentially be presented to TPSAC.

On March 11th, 2015, Swedish Match North America submitted eight General brand snus premarket tobacco product applications to FDA seeking authorization under Section 910(b). One snus product was a loose product, and the others were portioned snus products.

As per Section 911(f)(1), any MRTPAs must be referred to TPSAC for discussion. In the case of PMTAs, the FDA or the applicant may refer applications to TPSAC for discussion, but no requirement exists. Many of the issues for TPSAC discussion regarding the MRTPAs for the General brand snus overlapped with the potential issues related to premarket authorization consideration, such as considerations of health impact from these snus products. Therefore, FDA determined that there was no issue specific to the PMTAs that would require a second TPSAC meeting to discuss the same products.

FDA utilizes the PMTA process to evaluate the morbidity and mortality associated with tobacco product use. In evaluating how marketed authorization for these Swedish snus products impacts the current market, FDA considered the possibility that a PMTA order may increase use and initiation

of snus due to its perceived favorable profile. Based on the product's characteristics and properties, the impact on health, impact on smoking cessation, impact on snus initiation and uptake, and impact on current smokeless tobacco users, they were all considered in totality.

In discussing the manufacturing products, these products are produced with a voluntary proprietary manufacturing process to ensure quality that distinguishes Swedish snus from other types of smokeless tobacco products, including snus-like products sold in the current U.S. tobacco product market. The principal components of the standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents, including certain carcinogens and the finished products.

Product evaluation took into account many aspects, including evaluating ingredients, design parameters, and manufacturing. This slide describes examples of parameters evaluated, such as tobacco cut size, tobacco moisture, portion mass, length, width, thickness, and pouch paper porosity and permeability, as well as wicking. Product stability, heat

treatment, additive fermentation, storage, and microbial concerns were also evaluated in this process.

The FDA samples testing and FDA inspections allow for confirmation of information submitted in the applications. FDA conducted onsite clinical and manufacturing inspections of domestic and foreign clinical sites related to the manufacturing of these products. FDA inspected clinical study sites, including Indianapolis, Indiana and Serbia, manufacturing sites in Sweden, and at Swedish Match North America laboratory facility in Sweden.

Manufacturing, product analysis, packaging, distribution, recalls and complaints, shipping, laboratory accreditation, validations, raw data, and procedures were evaluated at the different sites. The clinical site inspections included the review of paper and electronic source data, electronic case report forms, and administrative files.

The Swedish Match North America smokeless tobacco products have significantly lower levels of NNN and NNK compared to over 97 percent of the smokeless tobacco products currently on the U.S. market. The products in the Swedish Match North America PMTAs may decrease the individual risk among current smokeless tobacco users due to their favorable toxicological profile

without posing increased risk to the general population.

Levels of other HPHCs, including arsenic, cadmium, acetaldehyde, crotonaldehyde, formaldehyde, and benzo[a]pyrene are similar to or lower than levels of smokeless tobacco products currently on the U.S. tobacco product market. And certain HPHCs have been identified as constituents of more toxic concern in the smoke of combusted tobacco products as compared to smokeless products.

Swedish Match North America provided a comprehensive review of published literature on the health effects related to Swedish Match snus use and specific disease states. In general, the literature presented confirms that individual snus user health risks are lower or at least no greater than those associated with cigarette smoking.

The applications provide evidence that use of the products which are the subject of these applications is not likely to be associated with lung cancer, COPD, or chronic respiratory diseases. Data are insufficient to support a lack of association between product use of these products and other disease endpoints specified in the applications.

With regard to oral cancer risk, the scientific evidence provided in this application suggests that the risk from these

proposed Swedish snus products is lower than the risk from smoking cigarettes or use of other smokeless tobacco products.

The literature presented indicates that Swedish snus use does have a negative effect on dental health. Gingival recession was noted at increased frequency in several studies even in younger subjects exposed for short periods of time. But overall, the evidence supports that the use of these products has a lower risk of disease for the individual user than use of other smokeless tobacco products. Use of these products is not associated with significant second or thirdhand exposure, which decreases disease risk for the general population.

Data indicate there is limited switching behaviors from exclusive smoking to exclusive smokeless tobacco use and that the adoption of snus use in the U.S. is low and therefore unlikely to lead to use of other tobacco products.

It is anticipated that with the marketing of the proposed products as described in the PMTAs, there is a low likelihood of nonuser uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

In summary, when used exclusively instead of cigarettes, these snus products offer lower risk of developing respiratory

diseases and certain cancers. Assuming that the only users of these products are persons who would have used other smokeless tobacco products currently on the U.S. market, individuals using these products with lower NNN levels could decrease their excess cancer risk.

Where we may see the greatest impact is among current users of smokeless tobacco products. Given that the full characterization, manufacturing, processing, and labeling of the eight snus products are considered to be acceptable and their toxicological risk is considered to be significantly lower than that of similar products on the market for current smokeless tobacco users, it is likely appropriate to allow access to these products. Otherwise, available options would be limited to the existing grandfathered products and similar products.

Given these reasons described, authorization of these products was issued to Swedish Match North America.

Thank you. Any questions?

DR. HUANG: Questions for Dr. Chen?

Yes, Dr. Weitzman?

DR. WEITZMAN: Thank you very much. It really helped me understand the process.

When one does a literature review on a new product, there is a limited literature. So when you say a review, does it entail a systematic review or a meta-analysis? Do you actually make decisions based on the findings of one or a handful of studies?

DR. CHEN: So there are no requirements in terms of the PMTA applications because we don't have regulations at this time. However, there are the statutory requirements.

And in terms of literature review, we expect that the applicants would do a publicly available literature search and look for any information that is reasonably known to the applicant about their product as well as similar products, for example. So we wouldn't expect there to be much data on any specific product. And especially if it's a premarket tobacco product application, their product may not be on the market yet.

In the case of ENDS, it's a little bit of an unusual situation where we do have a compliance period where there's ENDS products currently available, for example. And so you might have some studies done on a particular ENDS product. But there may be information -- not much information on a specific product, but there may be information on that category of

products that would be reasonably available to an applicant for them to do a survey of the literature available.

Now, of course we'd appreciate a systematic review, and we've talked about that in the information and seminar, but I think that any sort of literature search should be methodological and systematic in a way that we can reproduce it and understand that both positive information and negative information would be presented in a fair manner.

DR. HUANG: Yes, Dr. Weitzman again, sure.

DR. WEITZMAN: So does the FDA do its own literature review? And the other question is how do you reevaluate things down the line when there is an emerging literature that may or may not corroborate the findings that you were presented with in the application?

DR. CHEN: Absolutely. As FDA scientist, we try to stay up on the literature for all different products. And so we do do regular updates on the literature available on tobacco products. And so when something comes in, we would, of course, do our own search to make sure that there is a comprehensive analysis that's done.

And in terms of looking at the products, we need to continue to ensure that the product is appropriate for the

protection of public health. Remember that there are postmarketing reports that are required along with the authorization, and in doing so, the science may change. And we'll look at the science at the time and the material submitted and determine when we do the annual review, for example, that the product continues to be appropriate for the protection of the public health.

DR. HUANG: Dr. Ossip?

DR. OSSIP: Thank you for this presentation. I agree it was very, very helpful.

I have a question about the temporal relationship between PMTA and MRTPA reviews.

DR. CHEN: Um-hum.

DR. OSSIP: You had mentioned that because of the overlap in issues discussed by the TPSAC for the MRTPA and the issues involved in the PMTA, that you didn't -- you opted that it was unnecessary to forward the PMTA to the TPSAC.

So do I gather from that that the two can occur concurrently or they can occur in either order, could be PMTA and then an MRTPA? They could occur concurrently or could occur in the opposite order?

DR. CHEN: Right. They're not necessarily linked. I

mean, and I think one of the presenters had a slide before that a company, an applicant can come in for a modified risk claim with a product that is grandfathered, for example, or on the market through SE or PMTA. So there's different pathways that a product could be on the market and then a company could seek a risk reduction claim, for example.

Or they could be a product that's not currently on the market, and they may choose to submit a PMTA and an MRTPA at the same time, or it could be at different time points. In this case, the MRTPAs were submitted initially, and then following that, the PMTAs were submitted, and so there was an overlap in the submissions. So it really is up to the applicant. The timing just happened to work out in this case.

DR. HUANG: Dr. McKinney first?

DR. McKINNEY: Thank you, Dr. Chen.

My question is related to the public health considerations. When we think about nonusers using -- we use the term "tobacco product," but in this case, it would be the snus product -- what's an acceptable level, and will the Committee be giving some guidance on that as a review of a PMTA? And then I had another question, slightly different. You want to answer that one first --

DR. CHEN: Well, let me answer one question at a time.

DR. McKINNEY: Okay.

DR. CHEN: Otherwise I might forget the first one.

We would probably look to the Advisory Committee to provide their insight and recommendations to the FDA. There is no number, percentage of acceptable initiation, for example, and I think that what's important is to understand that the PMTA is looked at at the totality of information. And so there's no such thing as, you know, winning on all fronts, for example, or losing on any one front makes a application go to a denial.

I think it is important to consider all the different aspects that go into it. And overall, at the end of the day, looking at the totality of information submitted, do we think that there is a, you know, net benefit and reduction in the morbidity and mortality, right, of the population as a general matter.

And then you had a second part?

DR. McKINNEY: Is it okay?

DR. HUANG: Yes, Dr. McKinney.

DR. McKINNEY: Okay. Thank you.

And this question goes back to the PMTA and the MRTP and

what the TPSAC sees. Based on your experience, is there different information in those applications and some information in a PMTA that may be useful for the TPSAC to see as they address the questions that the FDA has?

DR. CHEN: We don't have a lot of experience with PMTAs and MRTPAs, but it's also up to the applicant because the applicant may submit different packages for the PMTA and the MRTPA, so in which case, you know, different materials may be submitted. But in general, we will prepare a briefing package that summarizes what we think are the most critical components and studies that should be presented and reviewed by the Committee. And in the case of the MRTPA, there needs to be a full redacted application provided, so there's that as well.

DR. HUANG: Dr. Bierut?

DR. BIERUT: Thank you for this presentation.

I have kind of a process question. So, of course, we want to move forward with the best science available and make these judgments. And you talked about a review process. What happens in this review process if we find out that we were incorrect with our assumptions and there is actually increased risk?

DR. CHEN: Again, that's the reason why I think the

statute calls for continual reassessment of whether the product continues to be appropriate for the protection of public health. And like we said, at the time, we make our decisions based on the available science. And over time, the scientific information, you know, the knowledge base grows, and we may find that what we thought to be a less risk product may not actually turn out to be so. And in that case, we will then take measures to address that.

DR. HUANG: Dr. Giovino?

DR. GIOVINO: I thank you as well.

I have two questions, if I might. I agree that initiation is a difficult -- well, it would be a problem. When I think about it, I realize that there are some young people who would initiate no matter what we did. And if it's possible that they initiate with a Marlboro that might be 100 times more dangerous than a snus product or, you know, 50 times, some, you know, order of magnitude more dangerous, and if those kids would have gone to Marlboro anyhow or Camel or Newport or whatever, then by going to the new modified risk product, that's a public health win even though they've initiated tobacco.

Now, the crucial component to this conceptual issue is how do we know? How do we estimate that? And I don't -- I haven't

quite thought that through well enough. But I don't -- I guess my first question is has FDA actually factored that in? And if so, what have you come up with?

DR. CHEN: Well, I want to just clarify that my discussion is about PMTAs, and you were talking about modified risk products. And that would be Dr. Apelberg's discussion later.

DR. GIOVINO: I can save that for Ben.

DR. CHEN: Yes. But what I can talk about is just that we do rely on publicly available information, such as national surveys. And I think that while we may not be able to oftentimes look at specific products within a national survey context, we can look at general trends of product types, for example, and that may help to boost our understanding about a specific product within that category.

DR. GIOVINO: Sure.

DR. CHEN: So, for example, FDA has the PATH Study. And that hopefully will give us more and more information. Given it's a large longitudinal study, we can get good estimates on transitional behaviors as well as use and quitting behaviors, etc. So I think we rely on available information to help us make the best decisions possible.

DR. GIOVINO: And the other side of that question is that

there are some kids who never would have started who might start with this less dangerous product and maybe use that their entire lives or for decades. And then there are some kids who would have never have started who might start on the less dangerous tobacco product and then progress to Marlboros, Camels, or Newport or whatever, which, of course, which is a major public health loss.

I think David Levy incorporates such concepts into his models, and there's a lot of -- but it's -- as best I can tell, it's still a guessing game, you know. We're still making our best judgments on that.

So my second question, if I may, is -- the harmful or potential harmful constituents, your proposed list online is dozens long; is there a minimum panel that you require applicants to, you know, address?

DR. CHEN: So there are no requirements because we don't have regulations in place, but I think that it depends on the product. And so applicants would then determine based on their product type what HPHCs would be appropriate to evaluate based on what the product is.

I don't know if Dr. Ashley or Dr. Holman have any other comments to add to that?

DR. HOLMAN: No, I think that's correct. I mean, there are no set requirements. However, based on the specific products and what we know about that product, that class of products, we would certainly -- FDA would certainly be looking for, thinking about certain HPHCs and looking for those in the application.

If they weren't in the application, you know, that may prevent us from issuing a marketing order. It may mean that we go back to the applicant to ask them if they had that data and they just didn't provide it to us. We do have some samples that are provided to us for analysis. Maybe we do analysis of certain HPHCs that weren't provided in the application. So I think there are different avenues that we could pursue, but it is really a case-by-case basis.

And getting to your first question, too, just to add to what Ii-Lun said, we keep using the word net, net, net, net effect. I mean, there are a lot of different factors that we need to consider, that you guys need to consider as you have applications before you. And it is very complicated. It is very challenging to weigh out what the totality of effect will be, because there will be wins likely in some areas, as you said, and there will be losses in other areas. And so we have

to do, and what we ask you to do, is provide us recommendations for how to best navigate those often in the absence of, you know, the type of data we like to have on the specific product of interest.

And so, as Ii Lun was alluding to, a lot of what we do is try our best to extrapolate from the datasets we do have available. The best we can, that we think we can extrapolate and bridge to the particular product of interest and make some sort of determination.

And I agree with you that modeling could be very useful in that regards, and I think there a number of different folks working on such models. And, you know, once we get some robust models that are validated, that would certainly help us tremendously in making these types of decisions. But, you know, unfortunately, I think a lot of those models are still in development and not necessarily fully validated.

DR. GIOVINO: Certainly, and I'll just make one more comment real quick because -- and I agree with net. And I think a lot of it -- a lot of what happens depends on how it's marketed, and that will be crucial.

DR. HOLMAN: Yeah. And again, one of the advantages we have here with PMTA and MRTPA is that we have postmarket

surveillance, and we have the legal authority to remove products from market if justified. And so that actually is a powerful tool that we have at our disposal.

DR. HUANG: Dr. Fagan?

DR. FAGAN: Did you want to go and ask --

DR. HUANG: No, go ahead. That was actually the point I was going to make in terms of the marketing.

DR. FAGAN: Oh, well, I'm kind of building off of the discussion here.

Thanks for the presentation, Dr. Chen.

So we know that different products have different effects and consequences for different populations. And so just going back to this absence or the science base or not having enough evidence there, how is FDA taking into consideration the population impact for vulnerable populations who already have different consequences? And so how is that weighed into the decision making around population impact for vulnerable groups like pregnant women and children and communities of color?

DR. CHEN: Yeah. I think that I would address that as saying that, again, we ask that the applicant consider the population as a whole, and we do ask them to address vulnerable populations. It is mentioned in the draft guidance, and it is

up to the applicant to address these issues. And the FDA, as well as if it's referred to TPSAC, they will be asked to review that information and see if they agree with the conclusions made by the applicant as to whether it is appropriate for the protection of public health considering the population as a whole, including users, nonusers, vulnerable population, etc. So it is an open question.

DR. HOLMAN: Can I just -- one little piece to that. We do have guidance documents out there that we do talk about this. The other thing that we've talked about in some of these presentations is that we do have pre-meetings with applicants before they submit their application to us. And these are the types of issues we talk about with them, you know, what are the vulnerable populations that we're concerned about for the particular product, and what kind of data and information can they provide in their application to ensure that they do account for the effects of, you know, these products on those vulnerable populations.

DR. HUANG: Dr. Ashley?

DR. ASHLEY: And just one thing to add. We're going to have a discussion later on in the day specifically about what we did at the meeting we had 2 years ago. And I'm sure you

remember a lot of that discussion was about vulnerable populations. And so I would suggest you bring that up at that time as part of the overall discussion.

DR. HUANG: Dr. Ossip?

DR. OSSIP: I just wanted to follow up on some points Dr. Fagan had made, but I can save that for the later discussion today.

DR. HUANG: Dr. McKinney?

DR. McKINNEY: Yeah. I've heard pre-meetings mentioned a couple of times. And the question I have, is there a limit on the number of pre-meetings? I know you guys are looking at me like he's trying to give us a lot of work, but that's my question. Is there a limit on the number of pre-meetings you can have?

DR. HOLMAN: I mean, we don't have any regulatory limit clearly, but that being said, I mean, there's sort of a practical limit as to how much, you know, time and how much of our resources we can expend. And so we have put out guidance, and we certainly try to convey to applicants when they submit their meeting packages to us how to most effectively do that to best utilize the time that we're willing and able to extend in working with them to help provide guidance.

So it does vary, I think. There are some applications where we may only have one meeting, and there are others where we may have possibly more than one. But often we try to limit that because we have a number of potential applicants, and we only have so many resources to expend on those types of things.

DR. HUANG: Yes, Dr. Thrasher?

DR. THRASHER: Just thinking about the PMTA draft guidelines, can you say when you expect the guidelines to be finalized?

DR. CHEN: I'm not able to specify any sort of timeline at this point.

DR. HUANG: Dr. Weitzman?

DR. WEITZMAN: A number of the outcomes that we're speaking about are far in the future from initiation or when you begin to use them. When you talk about something like chronic obstructive pulmonary disease or lung cancer or pancreatic cancer, how -- I mean, the methodologic difficulties that those sorts of issues raise are quite daunting. How do you go about dealing with that?

DR. CHEN: Absolutely. No, we don't expect applicants to conduct, you know, 5-year studies, 10-year studies, even 15-year, and frankly, for that matter, you know, 6-month or

1-year studies. So we rely on, for example, biomarkers to the extent that they're available and able to inform us. And so we have had informational seminars talking about how we can evaluate acute as well as more chronic health impact by looking at biomarkers and extrapolating information from that.

DR. HOLMAN: And if I could add, we also, in some cases like the Swedish Match products, have evidence, long-term evidence from other countries. And so there's the possibility to extrapolate. I mean, the challenge becomes, then, how to bridge between those populations and our U.S. population, and those do create challenges. But there is an area where we can actually get some, you know, decades' worth of data to be able to evaluate products.

DR. HUANG: Dr. Ossip?

DR. OSSIP: I'll confine this to PMTAs, but I think it would apply to MRTPAs as well. If a product was approved for their PMTA, and postmarketing surveillance was being conducted, and there were a number of products, perhaps similar products that had been approved, but in the postmarketing surveillance for a single product or other research in the field, some additional consequence were identified that had not been part of, say, the traditional measures that had been done initially

at application or that were included in the surveillance, does the FDA have the authority to then go back to all of those previously approved products for marketing and --

DR. CHEN: You mean like a class effect, you know, product class effect was identified?

DR. OSSIP: Yeah.

DR. CHEN: Certainly, that could happen where if we -- if there's new information to determine a toxicity that was previously unknown is, you know, available for us to understand the impact of certain products and which all have this ingredient, let's say, have a detrimental impact, and it's not appropriate, then, yes, we should be able to go back to those specific products, you know, that whole class of products, and then go back and move -- work towards removing those products if they don't meet the definition of the statutory requirements.

DR. OSSIP: Okay. If I could follow up on that just for a moment, I think that will be important because I can imagine that particularly with novel products emerging, that, you know, we may not know what to look for quite yet, so --

DR. CHEN: Absolutely. We do the best we can --

DR. OSSIP: -- there may be a traditional panel that would

be --

DR. CHEN: -- at the time.

DR. OSSIP: But yeah, there may be emerging --

DR. HUANG: Dr. O'Connor?

DR. O'CONNOR: Yeah. I wanted to ask a question about PMTA in general and how it would apply to products that are sort of amalgams of things. So, for example, with ENDS, for example, you've got the liquid part and you've got the device part. Some places they're combined into one unit. Some places they're interchangeable. And so in, yeah, I understand in a PMTA, a manufacturer is bringing that forward. But is it a way of sort of here's the PMTA for the liquid, here's the PMTA for the device? Do they cross-talk to each other, or is there sort of a wall between them? Or is the entire product as used considered?

DR. CHEN: It's up to the applicant really. For example, if you have a e-liquid manufacturer, and they are focused on making e-liquids, they may submit a PMTA for their product. However, we're interested in understanding the e-liquid ingredients, for example. And so in the liquid state, you know, what are the ingredients, how it's made, but then also, once it's aerosolized as it's intended to be used, what would

the user exposures/nonuser exposures be. So in that case, they may need to pick a product that they can use in combination with their e-liquids and provide some information so we have an understanding what the users may be exposed to.

And there could be also manufacturers that make a complete ENDS product, and in which case they would submit all the information pertaining to their product. So it's variable. There's different pathways.

So an ENDS product that is just the aerosolizing apparatus, they could potentially come in with a PMTA. Then they might have to choose an e-liquid to test, and it would be up to their, you know, up to their discretion as to what products they pick to demonstrate the properties of their product.

DR. HUANG: Any other questions?

(No response.)

DR. HUANG: All right. Thank you, Dr. Chen.

DR. CHEN: All right. Thanks.

DR. HUANG: Okay. So we will now break for lunch. Committee members, please remember there must be no discussion of the meeting topic during lunch either amongst yourselves, with the press, or with any member of the audience.

Now, you know, because of some concerns maybe about flights and weather, we're proposing taking a 45-minute lunch to save time. Does that sound good?

So we will reconvene again in this room 45 minutes from now at 12:45. Please take any personal belongings you may want with you at this time. Thanks.

(Whereupon, at 12:00 p.m., a luncheon recess was taken.)

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

(12:51 p.m.)

DR. HUANG: We'll get started. Hope everyone had a good lunch. So, again, we're a little ahead of schedule, which is good. So next on the agenda is Dr. Apelberg to talk about the MRTP marketing decisions.

DR. APELBERG: Good afternoon, everyone. My name is Ben Apelberg. I'm the Director of the Division of Population Health Science in the Office of Science. And today I'm going to be talking about modified risk tobacco product marketing decisions.

So here's just a brief outline of what I'm going to discuss today. I'll start just revisiting the statutory framework for modified risk tobacco products, just highlighting a few areas. And then I'll turn to how this framework was applied to the Swedish Match North America MRTPAs, then talk about the decisions that FDA made on these applications. And then, finally, I'll provide a summary of the TPSAC meeting that was held to discuss these applications. And that would lead into the discussion later about the process and what -- feedback from the Committee with respect to that process.

So just getting back to the statutory framework, so this

is something that Stephanie Redus talked about in her presentation. But just to reinforce the definition that's presented, here is the definition of a modified risk tobacco product in Section 911 of the Federal Food, Drug & Cosmetic Act.

And it's defined as a tobacco product sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. And this includes products whose label, labeling, or advertising represents, either explicitly or implicitly, that the product is less harmful or presents a lower risk of tobacco-related disease, or that the product or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain or is free of a substance. This also includes products which use the descriptors "lights," "mild," "low," or other similar ones.

And just to reinforce the standard for modified risk tobacco products, in determining whether an order should be issued, FDA must assess whether it has been demonstrated that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of

the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

The Act also describes a special rule for certain products. This is 911(g)(2). And this is what's been referred to as Exposure Modification Order.

In this case, it allows FDA to issue an order if, among other things, it's determined that it would be appropriate to promote the public health; that the label, labeling, and advertising in this case is limited to a claim that either the product does not contain or is free of a substance or that it contains a reduced level of a substance or presents reduced exposure; and that scientific evidence is not available without conducting long-term epidemiological studies for an application to meet the standard for a risk modification order; also, FDA must determine that the scientific evidence that is available demonstrates that a reduction in morbidity and mortality in future studies is reasonably likely.

So when we think about the evaluation of an MRTPA, what I've laid out here is a few key overarching steps. Now, each of these steps really involves the evaluation of many specific questions, which draws from multiple scientific disciplines.

So just to remember, in evaluating an MRTPA, CTP has to consider the product with the proposed specific modified risk information. So the first question really is related to whether the modified risk information that's proposed to be communicated is scientifically accurate. So is there adequate scientific substantiation of the proposed modified risk information that the applicant has submitted?

Second, will the MRTPA significantly reduce the harm and risk of tobacco-related disease to individual tobacco users?

Third, how do consumers' perception, understanding, and comprehension of the modified risk information impact potential benefits and harms?

And then, ultimately, what are the potential benefits and harms to the health of the population as a whole, once again taking into account the impact to users and to nonusers.

And then just to reinforce something that Stephanie Redus said in her presentation, just a reminder that an MRTPA order is for a specific product, not for a class of products. And the evaluations are the context not only of the specific product but also the specific modified risk claim or modified risk information that a company is proposing to communicate. Therefore, as a result, the form and the wording of the claim

can have a critical impact on the final decision.

So that's just some of the background context. Now I wanted to turn to how this framework was applied to the Swedish Match MRTPAs.

So on June 10th, 2014, FDA received modified risk tobacco product applications for 10 General snus products listed here. These products vary by portion size, flavor, pouch versus loose snus -- loose tobacco. And although applications for 10 products were received originally, the company withdrew 2 products, the 2 that are asterisked here, leaving a total of 8 products for the MRTP review.

The applications themselves contained information from various types of scientific studies. This included product analyses focused on the chemistry, engineering, and microbiological properties of the products; toxicological assessments; pharmacokinetic studies; clinical trials, and in this case really focused on the impact of these products on cessation among smokers; epidemiological evidence on both of the long-term health risks from literature in Sweden and Norway as well as patterns of behavior in those countries; a consumer perception study; statistical modeling; and then a sort of broad overview of a plan for postmarket surveillance.

The specific requests that Swedish Match North America submitted were for the removal and revision of existing smokeless tobacco product health warnings. So, in particular, the applicant requested that it be allowed to market these products as modified risk tobacco products by omitting two of the currently required warning statements for smokeless tobacco products. This includes the warning that says "Warning: This product can cause gum disease and tooth loss" and "Warning: This product can cause mouth cancer."

The applicant also requested to revise a third warning statement from a "Warning: This product is not a safe alternative to cigarettes" to "Warning: No tobacco is safe, but this product presents substantially lower risks to health than cigarettes." And then the applicant did not request to change the fourth currently required warning, "Warning: Smokeless tobacco is addictive."

So in their applications, Swedish Match North America asserted a number of things. One, that the General snus products that were the subject of these applications conform to the same standards as the products used in Sweden and Norway, which, among other criteria, as you heard from Dr. Chen, establishes maximum levels of certain harmful constituents in

the products. So to support this assertion, they provided information about the engineering of the products as well as chemical and microbiological properties.

The applicant also provided a broad review of existing literature on the health risks, epidemiological studies associated with the use of snus products in Sweden and Norway.

The applicant also argued that the evidence demonstrated that in Sweden, where snus use is more prevalent, smoking rates among men and rates of tobacco-related disease and death are lower than in other developed countries. And this movement from smoking to snus use was attributed to a grass roots movement among Swedes to switch from smoking cigarettes to traditional snus products.

So in evaluating these applications, FDA completed a number of different steps as part of the review process. So this includes reviewing the full submissions as a multidisciplinary team with expertise in a range of different disciplines you can see listed here.

During the review, a clarification was requested and received from the applicant on specific topics and questions that arose during the review. The review team reviewed public comments received on the redacted applications. The Agency

convened the TPSAC to deliberate on key issues and integrated findings from the Committee into the overall review. And then FDA ultimately evaluated all relevant evidence to determine whether the statutory requirements were met.

So now I'm just going to go through some of the key findings of the review. This can also be found in the technical project lead review, which is on FDA's website along with additional information related to the applications.

So just to reiterate, for the finding on gum disease and tooth loss, so the applicant requested to omit from the label and advertising of these products the warning that the product can cause gum disease and tooth loss. This warning is currently required for all smokeless tobacco products generally, and smokeless tobacco products have been required to bear a warning related to gum disease and tooth loss since 1986.

Omission of this warning represents an implied modified risk claim that the eight General snus products that were the subject of these applications, unlike other smokeless tobacco products, cannot cause gum disease or tooth loss. It should be noted that this wasn't an implied claim or an explicit claim that the products pose a lower risk of gum disease or tooth

loss as compared to other smokeless tobacco products or other products in general.

FDA evaluated all the evidence and determined that the evidence did not support this implied claim. To the contrary, studies submitted by the applicant as well as others received by FDA indicate that the use of these snus products increased the risk of certain outcomes classified as gum disease or tooth loss or precursors of gum disease or tooth loss.

FDA also determined that there was little biologically plausible reason to expect that the outcomes related specifically to gum disease and tooth loss resulting from the use of these products would differ from those resulting from the use of other smokeless tobacco products. Indeed, given that these snus products, like other smokeless tobacco products, were found to cause delayed soft tissue wound healing, these products would not be expected to differ with respect to these disease outcomes. Overall, the evidence, then, supported that these products can cause gum disease and tooth loss, and therefore, the claim was not substantiated.

With respect to mouth cancer, so once again, the applicant proposed to omit from the label and advertising of these products the warning that says, "Warning: This product can

cause mouth cancer." All smokeless tobacco products are required to carry this warning presently, and there has been a warning related to mouth cancer required since 1986. So, once again, omission of this warning represents an implied modified risk claim that these products, unlike other smokeless tobacco products, cannot cause mouth cancer.

Here, FDA reviewed the available epidemiological evidence as well as toxicological evidence and found that although there is a lack of consistent association between the use of Swedish snus and risk of oral cancer, the most recently published study in the applications reported a large and statistically significant association. Some of the reasons for lack of a consistent association may be due in part to variability in the definition of oral cancer, variability in the exposure definitions in these studies, and other potential limitations.

From a toxicological standpoint, review of available data indicates that the use of these products would post an oral cancer risk. Although the products contain significantly lower levels of the tobacco-specific nitrosamines, particularly NNN and NNK, than other tobacco products, no threshold dose has been established for either NNN or NNK carcinogenicity. The applicant did not provide toxicological evidence to the

contrary, thus leading to the conclusion that the levels present in these products carry increased risk of carcinogenicity relative to nonuse.

Therefore, taken as a whole, FDA determined that the available science supported the statement that smokeless tobacco products in general and these products in particular can cause mouth cancer. And, therefore, the claim was not substantiated.

With respect to the finding on relative risk to cigarettes, the scientific information provided by the applicant demonstrated that there is evidence to support that exclusive use of these products as compared to smoking cigarettes may significantly reduce harm and the risk of certain tobacco-related disease to individual tobacco users.

For example, there are clear substantial differences in the risk of certain major tobacco-related diseases such as lung cancer and respiratory disease. The reduction in health risk to an individual is dependent on patterns of use of the products, in particular, whether individual users switch completely to the use of the products from cigarettes.

FDA reviewed all available evidence and determined that the evidence partially substantiated the proposed modified risk

claim.

There are a few other key findings that I wanted to communicate to the Committee. Many of these are related to the issues that were brought to the Committee 2 years ago.

FDA determined that the information on the behavior of the Swedish and Norwegian population with respect to snus-type products has limited applicability to the U.S. population. So snus products are currently available in the U.S., but there has been a very low use of similar types of products by U.S. tobacco users.

Snus products are much more popular among Swedish tobacco users, and as the applicant acknowledged, snus hold a status as a traditional Swedish and Norwegian product. Swedish Match North America described a historical grass roots shift away from smoking to snus use that occurred in Sweden particularly among male smokers but did not provide evidence or information to suggest that a similar process could or would occur in the U.S. population. In contrast, recent research indicates that U.S. cigarette smokers did not particularly find snus to be an appealing alternative to cigarette smoking.

It's also important to note that the labeling and marketing of snus in Sweden has not referred to the product as

reduced risk.

With respect to the consumer perception study, FDA determined that the study itself did not provide sufficient insight as to what consumers understand about the risks of using the products after viewing the modified risk information, particular in the context of a warning. This was due to a number of deficiencies, including that the applicant did not provide evidence regarding how the removal of a warning would impact consumer behavior or comprehension.

For the revised warning statement, the applicant did not assess the impact of the context of the modified risk information, so whether in the context of a warning or outside of a warning, and the stimuli included in the study did not reflect the actual proposed or revised warning statement verbatim.

And then, finally, with respect to population modeling, the applicant did model a number of different scenarios of impact to users and nonusers. Some of these scenarios resulted in population health benefits, some in population health harms. However, there was inadequate evidence as to which scenarios were more or less likely and how best to kind of weigh the likelihood of those scenarios.

So those were some of the key findings with respect to the applications. And then on to FDA's decision.

So with respect to the request to remove the gum disease and tooth loss warning, FDA concluded that Swedish Match North America did not demonstrate that, as actually used by consumers, the product would significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole. Therefore, this request was denied.

With respect to the other two requests, to remove the mouth cancer warning and revise the "not a safe alternative" warning, FDA determined that, in their present form, the applications didn't contain sufficient evidence to satisfy the modified risk standard. However, the applications could be amended in several ways which could provide evidence to support issuance of modified risk orders. And some of those include changing the proposed claims, supplementing with additional evidence, or conducting new studies.

So on these two requests for which the FDA has deferred final action, the Agency does believe that the applications could be amended in such a way that could support issuance of modified risk orders.

And I just wanted to make it clear what while the FDA isn't authorizing these specific products as MRTPs at this time, the lessons learned through these first applications do provide key insights for a potential path forward through an amended application and for others considering submitting an application and that the FDA is committed to authorizing modified risk tobacco products for any company which submits adequate data demonstrating that the standard has been met.

That's kind of a summary of the review process and FDA's findings and determination. I now wanted to spend a little time just describing the process that FDA underwent to hold the TPSAC meeting in April of 2015, where these applications were discussed. And then hopefully that will lead into -- will be a useful lead-in to the discussion that the Committee will be having about the experience of that meeting and recommendations for information that would help in future meetings.

So pursuant to Section 911(f) of the Federal Food, Drug & Cosmetic Act, FDA referred these MRTPAs to the TPSAC, and the TPSAC discussed the applications during an Open Public Committee meeting held on April 9th and 10th of 2015. At the meeting, the Committee discussed the MRTPAs, including the adequacy of the scientific evidence to support the proposed

modified risk marketing.

Before I get into the specifics of the meeting, I just wanted to provide a little more context for the scope of TPSAC meetings to deliberate on an application.

So, in conducting its review, FDA will review the entirety of the materials included in an MRTP application. Although the entire applications are referred to the Committee, the presentations to the Committee may not include all issues relevant to the final regulatory recommendation. Instead, these meetings are intended to focus on issues identified by the Agency for discussion by the Committee. So, based on its review, FDA will identify critical scientific issues to bring the TPSAC for discussion directly related to the factors that FDA must consider when taking an action.

So for the April 2015 meeting, FDA brought forward a number of topics to this 2-day meeting for discussion, and a high-level summary is listed here. So with respect to the relative health risks to individuals, FDA brought to TPSAC questions related to the association between snus use and tooth loss and gum diseases, oral cancer, and the risks of snus in general compared to cigarettes.

With respect to initiation and cessation, FDA brought to

TPSAC questions related to the applicability of the Swedish experience to infer impacts to the U.S. population.

And with respect to the comprehending the modified risk information, FDA brought to TPSAC questions related to understanding the impacts of providing modified risk information in the context of a warning. And then FDA also sought recommendations from TPSAC on postmarket surveillance and studies should an order be issued.

So prior to the TPSAC meeting, the Committee was provided with the full, unredacted application, which was over 100,000 pages. And the Committee also received FDA background material. So this included a 65-page briefing document. This described FDA's preliminary review findings and draft topics for discussion. The package also included the MRTPA draft guidance for industry and then the statutory language in Section 911 of the Federal Food, Drug & Cosmetic Act. Written submissions to the Committee from the public were also provided to the Committee. And the applicant, Swedish Match North America, provided a 78-page briefing document as well.

The meeting participants included the eight voting TPSAC members at that time and three industry representatives. In addition, three ex officio members representing other federal

agencies were in attendance. The meeting also included scientists with a particular expertise in the areas of focus of the TPSAC meeting. So this included Dr. Paolo Boffetta, physician and epidemiologist with experience in smokeless tobacco use and cancer risk, and Dr. Scott Tomar, a dentist and researcher who studied the behavioral patterns and health risks of smokeless tobacco products. The meeting also included FDA staff and representatives for the applicant, who presented on various topics.

Just to give you a sense of the types of presentations, so Swedish Match North America provided an overview of their submission; a summary of the scientific literature review conducted by ENVIRON focused on characterizing the epidemiological evidence describing Swedish snus and health effects; a summary of the findings from the company's clinical trials, premarket consumer perception study, and the population modeling; and the applicant also presented on their voluntary GOTHIATEK standards.

FDA made several presentations to the Committee related to topics for discussion at the meeting. These included an overview of the statutory framework for MRTPAs and a summary of FDA's scientific review process. The remaining presentations

focused on particular aspects of FDA's review of the submission, and you can see the title of those slides and the content here. These really focused on the different questions and topics that were brought to the Committee.

Comments from the public were also made available to the Committee in several ways. So as you've already heard, these MRTPA applications that are accepted and filed will be made available for public comment, and so FDA summarized the scientific comments received through the docket at the TPSAC meeting. FDA solicited written comments in response to the TPSAC meeting announcement, which were also provided to the Committee in advance. And then Day 2 of the Committee meeting provided an additional opportunity for oral public comment.

And so, finally, just to kind of wrap this up, the information gained from discussion at the TPSAC meeting plays an important role in FDA's evaluation and determination. So TPSAC deliberation and voting are weighed in the evaluation of the evidence. Although the TPSAC votes are non-binding, they do inform FDA's assessment and determination. The findings from the Committee are integrated into the overall review and included as part of the technical project lead review, which summarizes the FDA's decision in the scientific argument.

So, as a result, we're interested in hearing from the Committee in the next session about the experiences at the 2015 meeting and also what information and structure would make future meetings to discuss MRTPAs and PMTAs as productive and informative as possible.

So, with that, I'll end my presentation, and I'll be happy to take any clarifying questions.

DR. HUANG: Thank you.

Any questions for Dr. Apelberg? Yes, Dr. Thrasher?

DR. THRASHER: Yeah. I'm just wondering, in evaluating labeling and advertising, do you all consider packaging to be part of advertising?

DR. APELBERG: Yes. You mean what's on the pack is what you're talking about?

DR. THRASHER: Yeah, what's on the pack, even the design of the pack, the structure of the pack, colors on the pack, words on the pack, everything on the pack and in the pack.

DR. APELBERG: Yeah. I mean, in the MRTPA submission, it requires samples of packaging, copies of samples of packaging, labeling, advertising that would all play into FDA's evaluation. So we're looking at the information that's being communicated, proposed to be communicated.

DR. HUANG: Dr. McKinney?

DR. McKINNEY: Thank you very much. During your presentation, you mentioned amended applications. Can you say more about that, and will the TPSAC be reviewing those applications? And more broadly, when there is a modification to a product that goes through a PMTA or an MRTP, how will that be handled?

DR. APELBERG: Yeah. So the first question related to amending applications, so yeah, one of the outcomes of this review was the issuance of these response letters in which we communicated to the company that if they chose to do so, they could amend their applications. And we laid out the concerns or the issues that would be important to address.

We haven't definitively made a decision about whether, you know, if an amended application comes in, whether that would necessarily go back to TPSAC or not. I'm looking over there. You know, I anticipate it would also be based on the nature of that.

I guess, in this case, it would be -- I guess I'll go out and say it would be likely that we would bring it because, you know, especially if it's going to be related to different claims that have, you know, different implications. But that's

something that will be determined.

Your second comment was about changes that are made to products after they've received authorization. So it's really -- remember the MRTPA pathway is really about the specific modified risk information that's attached to a product that has some other type of authorization. So if a product came in through the PMTA pathway and an applicant wanted to change it, I believe they would have to submit a, you know, an amendment or -- I don't know what the right terminology is --

DR. CHEN: Right. At that point, if a product that was authorized through PMTA is on the market and the manufacturer modified it, it would be a new tobacco product. But I think that there could be a process by which, for example, you could provide the information about the modification and then cross-reference the original application so that everything else that hasn't changed would be cross-referenced materials and anything new. But then the new product is addressed as a whole in totality.

DR. HUANG: Dr. Giovino? Oh, sorry. Go ahead. Dr. Ashley?

DR. ASHLEY: Yeah, let me just try to respond to the first question. So we've not had the case where we've had an amended

application come in after a decision, you know, after we have issued letters already. So we are not sure exactly what would happen with that. It's going to -- the lawyers will have to determine whether what it says in the statute that TPSAC has to look at of an MRTPA, if that means that every new version they have to look at or just once.

So that's still, you know, that's still up in the air because I myself can see cases where an amendment may be really minor, and it could be that the determination is made that that doesn't need to come back to TPSAC. It may be that when the lawyers get involved, they say, yeah, every version has to come back to TPSAC. So we've still got to work that issue out.

DR. HUANG: Go ahead, Dr. Giovino.

DR. GIOVINO: And thanks for a good presentation.

Maybe I should know this, but when -- supposing -- I'll use a hypothetical. Supposing Swedish Match of North America comes back with a comparative claim and the Committee recommends it and FDA approves it; is that it? Or does it have to go back to Congress? In other words, did Congress give FDA the legislative authority to change a warning label? Because I thought the warning labels were congressionally mandated in 1986. So I'm just wondering, legally, what's the process?

Does FDA have legal authority to change the warning label now?

DR. ASHLEY: FDA does have legal authority to change the warning label. And I don't think we're going to spend time going into that detail on under what circumstances, things like that, but yes. But it was determined at FDA that what -- their request was a valid request. And so that's why we went through the process. We wouldn't have gone through the process if it was determined that it was illegal for that decision to be made, so --

DR. GIOVINO: Oh, I -- yeah, I figured that, but I just -- I'm glad you verified it. Thank you.

DR. HUANG: Yes, Dr. Thrasher?

DR. THRASHER: Yeah. My question is with regard to assessing consumer perceptions and understanding of modified risk information. And as I understand it, the Swedish Match application included an assessment where people just evaluate whether the message was clear or not. And I wonder if FDA has some standards or kind of gold standard measures that they would recommend for assessing consumer understanding of risk in general, modified risk in particular?

DR. APELBERG: Yeah. It's a good question. I mean, right now, there's -- we don't have any particular guidance or, you

know, regulations that lays out like when, you know, when doing a consumer perception study, here's what the expectations are. But this is something that when companies do, you know, come in for meetings, they have the opportunity to really lay out, you know, their goals and their plans for conducting consumer perception research. And, you know, FDA would provide, you know, very detailed feedback with respect to the design of the study, the measures, you know, and so forth.

I mean, there are definitely general principles that we want to be able to make sure that are being communicated, but then there's also obviously going to be some variation depending on the nature of the specific research questions and the goals of the study. So it is something that, at this point, you know, we as an agency try to be as constructive, you know, in terms of the direct feedback at meetings, but it's something that I think over time could develop into a more structured, more detailed communication about both principles as well as specific recommendations with respect to design.

DR. HUANG: Dr. McKinney?

DR. McKINNEY: I think I'm going to -- I keep pushing this button so much I might break it, but my question is relative to the mandated warnings and then if a modified risk tobacco claim

is granted. So that would be on the packaging as well as the warnings. And the question is, is the manufacturer expected to submit information in terms of how the consumer would perceive the mandated warnings as well?

DR. APELBERG: What FDA would like to see is that whatever specific modified risk information is being proposed and being communicated on the packaging or labeling, that that would be studied in the context in which it would be seen. So if it's on the pack, it would be in the context of having warnings on the pack as well, since those are statutory mandated, right? Because we want to be able to understand the impact on perceptions, understanding, comprehension, you know, in as a realistic sense as possible.

DR. McKINNEY: But the information is on -- the data that's, I guess, provided will be on the comprehension and understanding of the modified risk claim?

DR. APELBERG: Right, right.

DR. McKINNEY: And not on the mandated warning?

DR. APELBERG: Right, exactly. It's just the context, right? So you might have a randomized study, right, where you have people that, you know, see the pack the way it is with the warning, and then you see, you know, others who see the pack

with the warning and the modified risk information. But we want to be able to pick up if somehow the combination of those two things is changing the way people perceive that information.

DR. ASHLEY: The bottom line here is what the applicant is proposing, that's what needs to be tested. And that's kind of the important thing so that we can make that evaluation.

DR. HOLMAN: So I think what you're getting at is does the applicant have to demonstrate that consumers adequately understand the mandated warnings?

DR. McKINNEY: Yes.

DR. HOLMAN: The answer is no. I mean, we would be focused on evaluating how consumers understand the proposed modified risk warnings. Now, that being said, what Ben was trying to point out is, but that would be in the context of the mandated warnings as well. And so what we would want to understand is how do those warnings, for example, potentially impact consumer understanding and comprehension of the proposed modified risk warnings?

So not necessarily directly measuring, you know, consumers' understanding of those required warnings, but again, in the context of the overall packaging, how does that

influence, potentially, the modified risk warning?

DR. HUANG: Any other -- oh, yeah, Dr. King?

DR. KING: I have a question related to the standard for modified risk -- and in the one slide, it underlined -- as it is actually used by consumers. And I'm wondering is that -- is it actually used by consumers, or does that account for as it's misused by consumers?

And so an example is some of these electronic products that are coming out. And if you use as directed, you aerosolize it directly to the user. But our nation's youth, in their infinite ingenuity, are doing something called dripping, where they actually put the liquid directly on the coil and heat it, and it's going to create different harmful and potentially harmful constituents than if you were to aerosolize as is originally directed or intended.

And so is that accounted for in your modified, you know, risk and when you do these types of assessments? Is it just the use as intended by the manufacturer, or is it potential misuse of the product that could potentially create other harmful and potentially harmful constituents?

DR. APELBERG: Yeah, I mean --

DR. KING: Do you know what I'm saying?

DR. APELBERG: Yeah. It's the broad. I mean, it's really understanding how people are using these products if they're already on the market or may use these products. If there's a great potential for misuse, what are the implications of that, you know? Obviously, the question of, you know, did people completely switch or did they cut down on cigarettes, or do they continue to, you know, smoke at the same rate? I mean, all of those factors are sort of playing into our understanding of what the implications are.

DR. HUANG: Any other questions? Dr. Weitzman?

DR. WEITZMAN: But if I understand this correctly, when an application is submitted, it's for a particular product and not for a class of products. So if you have a moving target that's moving as quickly as new alternative tobacco products are, does the FDA ever make a summary statement? If one were to, in fact, find that electronic nicotine devices did or did not help people stop smoking, would there ever be a statement that subsumed all the different versions of that?

And does the E -- FDA, I apologize -- does the -- so far what we've discussed today has been issues where the industry initiates the contact with the FDA. What are the situations in which the FDA, if there are, acts proactively rather than in

response to something brought by industry?

DR. APELBERG: Well, yeah. Well, I'll jump in and then hand it over to David. I mean, there's sort of a lot of things buried in that question. I mean, one of the things that FDA is doing is funding and conducting research generally and broadly. I mean, we have the PATH Study and, you know, a lot of other research. Of course, that's on products, you know, as a whole and product categories, and we're trying to, you know, develop and push the science forward.

I mean, with respect to an application, a company is, you know, going to submit for their specific product. Now, they might rely in part on the existing scientific literature for related products. And one of the things we've really tried to communicate to the applicants is to provide enough information to allow for bridging across those products, where an understanding of how -- you know, like what are the features of the product that may be more or less similar to those that have been studied so that we can, you know, understand the relevance of that information to the specific product that's being evaluated.

DR. ASHLEY: This particular meeting is about PMTA and MRTPA, and so we've kind of focused on those issues. FDA has a

lot of other authorities to use in different situations. It's just that trying to cover all of that in one meeting was just not realistic. So today we're focusing on PMTA and MRT, which are applications where the industry comes to us with a proposed application. There are other authorities that we can use in different circumstances.

DR. WEITZMAN: Does this Committee get involved in those other issues?

DR. ASHLEY: They may very well, yes, absolutely.

DR. HUANG: No other questions?

(No response.)

DR. HUANG: All right. Thank you, Dr. Apelberg.

So we're going to push through -- oh, we do? One -- oh, Dr. Johnson?

DR. JOHNSON: Sorry. But I just wanted to make sure I understood something. Previously, I think you said that when these studies are done with the devices, for example, ENDS devices, they're used as the consumer would use them, and then you said you also broaden that to potential misuse of the devices. How do you determine what is the scope of that, and why would you allow potential misuse of the product in a study designed to determine the safety of the device unless you're

looking at absolute physical safety of the device?

DR. APELBERG: Okay. If I'm understanding your question, so, you know, when I was talking about the language about "as actually used," so there's, you know, there's different lines of evidence that would come in to support an application. Yeah, you would have, you know, clinical studies perhaps where people are told to use the product in a certain way. But, you know, maybe most of them do, and maybe some of them don't, you know? How does the way they're using the product and what is the potential for misuse based on that information or even based on the design characteristics and features of the product? And if there is, you know, a great potential for that kind of misuse, like what are the implications of that for what individuals are exposed to, you know, what it means for risk?

And there might also be, you know, in the case where an applicant, you know, uses a body of evidence that exists in the published literature, for example, on ENDS, you know? If there is evidence in the published literature about misuse, understanding, okay, to what extent is that something that can be easily done with, you know, the way that this particular product is designed.

I mean, it's just one factor to consider in understanding,

you know, the risks of the product, right? So the products have some inherent risks, but that risk is presumably a function of how they're used, how frequently they're used, you know, the specific behavioral patterns.

So it's really, you know, my goal was just to communicate that those are factors that, you know, one would -- we would want to consider in, you know, overall in making the determination, not that you would get that information from one, just one particular study versus another.

DR. HOLMAN: If I could just add to that, I don't think we were trying to imply that there would be studies where users are forced to misuse the product. I think what we're talking about is the applicant should addressed, based on available information, how consumers may misuse their product, for example, dripping. And they should discuss and evaluate how they might prevent that misuse. Maybe they have a built-in feature on the product that wouldn't allow the consumer to drip.

Now, would they do a study and force people to try to drip? No, I don't think so. What they may do is a study where they give it to users and say how could you use this, how would you use it, and you know, just it may be even just asking them

questions rather than actual use. And I think that's what we were trying to get at, not that anyone was going to be forced to misuse the product to prove that it could be misused.

Does that make sense?

DR. JOHNSON: Thanks.

DR. HUANG: All right. Any other questions?

(No response.)

DR. HUANG: Thank you, Dr. Apelberg.

Okay. So, again, the last thing we have is to address these questions to the Committee. Now, some of the -- the first questions might be most relevant to the four that were at the April 2015 meeting, which I think Dr. Giovino, Dr. O'Connor, Dr. Fagan, and myself. But others can certainly provide any insights.

So the first question was: How was the information to the TPSAC prior to the 2015 meeting on the MRTPAs for the SMNA snus products helpful in preparing for the meeting?

So comments? Dr. Giovino?

DR. GIOVINO: I'll start. I thought it was very helpful. I thought it was the right level of detail. It was a lot of reading, but I thought it was the right level of detail. I did find myself looking up articles that it was discussing and

reviewing them. But I thought it was detailed enough to give us a handle and, you know, quite on target.

DR. HUANG: Other comments?

Dr. O'Connor?

DR. O'CONNOR: Yeah, I wouldn't disagree. I would say we got good summaries from both the applicant and the FDA in their review. I found some of the public comments that were provided also particularly helpful in sort of thinking about some of the issues involved. But it's a lot of stuff, and I don't know how you get around that, but it's a lot of stuff.

DR. HUANG: Yes, Dr. Ossip?

DR. OSSIP: If I may, I'm sorry I wasn't at that meeting, but I think we had been sent at least some portion of what had been sent to the Committee to take a look at before. And Dr. Giovino mentioned that he found himself looking up some of the articles, and I thought the review that was provided was extremely -- would have been extremely helpful had I been there.

I didn't see a place where there was an electronic link to the articles, and I wondered if it would be -- if that was not provided, if it would be possible to provide that because I can imagine that I'd be wanting to look up articles as well, and

that would make it much easier.

DR. GIOVINO: And I was going to actually make that suggestion later as well.

DR. HUANG: Good point.

Other comments?

Dr. McKinney?

DR. McKINNEY: Members that participated in that hearing, my question, do you feel that you had sufficient time to really adequately review the material? I know it was a lot, and there's a lot we had to review for this particular meeting, but do you think you had adequate time?

DR. HUANG: You know, I'll chime in. You know, and I would agree with Dr. Giovino, it was really the right level, I think, of detail, but then there was the access to everything, if one wanted it, through that locked sort of system.

You know, I actually thought there was -- I'm trying to remember the timeline exactly, in terms of how far before the meeting we received it, but there was, I think, certainly to go through the briefing materials that were received.

I mean, would you agree? I mean, it was a lot of material, but --

DR. GIOVINO: We were given plenty of lead time, if that's

your question. There was plenty of lead time to do the work.

DR. HUANG: Any other comments on the first question?

(No response.)

DR. HUANG: And I'll just again elaborate a little more. Yeah, just the briefing document, all of the guidance, you know, I think was, yeah, really very on target in terms of being helpful for the discussions, and then also having that access to the full application.

Let's move on to Question 2: How do you anticipate preparing for upcoming application review TPSAC meetings?

So comments? Dr. Fagan?

DR. FAGAN: Yes. I found myself pulling a lot of the literature as well, so I think for the next round, that's something that I will continue to spend some time on is pulling the data myself and looking at some of the results to evaluate them.

DR. HUANG: Other comments?

Oh, Dr. Ashley?

DR. ASHLEY: I just wanted to -- just for clarification, so you're talking about pulling results from the actual application and analyzing those yourself?

DR. FAGAN: There were articles that were related to the

application and claims that were being made, and so I found myself going into PubMed and pulling some of those papers to kind of validate what was being said and did it match with what was in the papers.

DR. HUANG: Dr. Giovino, yeah.

DR. GIOVINO: So I'm from Buffalo, New York, and every once in a while, we get word of a big blizzard coming. And so we sort of psychologically prepare for that. So it's my understanding that there's a million-page submission in the queue and there's another with 400,000 pages in the queue. So, I mean, I think that's public knowledge.

And so I realized that I may have to allot more time for the next meeting, but I'm kind of hoping that FDA will help us find the sweet spot again. But I think that's my biggest level of anticipation is having done it once, I think I'll likely have to allocate a little more time than I did the last time.

Now, I don't know if the volume of materials we get is proportional to the volume of materials that's submitted, but -- and for the life of me, I can't remember the number of pages that was submitted by Swedish Match in total, but I still think it might be -- it might take a little more of my time for the next preparation.

DR. HUANG: Dr. Weitzman?

DR. WEITZMAN: Well, I've spent a lot of my professional life in upstate New York, and I've never seen a snowstorm large enough to really give me the time to read a million pages.

(Laughter.)

DR. WEITZMAN: So I'm still trying to get my head around the process. When in the process of reviewing a product in anticipation of this meeting do we get involved? Is it after FDA staff has massaged this and brought it to some degree of closure and we're to discuss it and either agree or offer pieces of either advice or agreement or disagreement? Or do we start when you start?

DR. ASHLEY: Now, let me see if I can answer that a little bit. And if you were talking about timing, either Caryn -- Caryn can probably give actual dates and things.

So FDA will start our review. When we file the application, we will begin our review. We will begin the process. Hopefully, it won't be long, but we will make the process available to the public. That's something else we need to do. So we will do our review.

When we feel like our review has gotten to the point where we can communicate to you the basics of our review and what we

are finding, we will then provide a document to you which summarizes that. The company also will provide you a document with their basis and how they read the evidence. We will provide where you read the evidence. That way, you don't have to go through a million pages even if it is a long snowstorm in Buffalo, so -- because we will try to put together that document so that you've got the summary.

Now, we will provide that information to you. So if you come across something and you go, I just don't believe this, you can go to the full document if you want to. You're not required to do that. And so we will provide that to you well in advance so that you can review that. So when you come into the meeting, you will have that basis.

Then, during the meeting, the company will present to you, and they will present much of what you've already read. FDA will present to you much of what you've already read, and so that you will hear that a second time. You can ask questions. You can get clarification if you were going through it. And so it'll be that kind of a process.

DR. WEITZMAN: That's very --

DR. HUANG: Dr. Thrasher?

DR. THRASHER: Just for further clarification on that,

too, and so we'll also receive a list of the questions on which we are expected to vote before the meeting as well?

DR. HOLMAN: Yes. That's part of the meeting material.

DR. THRASHER: So when we receive the materials, we will also receive those questions?

DR. HOLMAN: Comment on timing --

MS. COHEN: You'll receive the draft questions, similar to what you received for this meeting, so you'll receive the -- you know, something very similar to what you'll see on the day of the meeting. But you'll receive the actual questions in their final version on the day of the meeting.

DR. HUANG: Dr. McKinney?

DR. McKINNEY: And would the industry also -- or the applicant receive those questions as well, and if so, when?

MS. COHEN: So everybody will receive those draft questions. They are posted on the web. The draft questions we post as soon as possible, but no later than 2 days before the meeting, and the industry will not receive those until the public does, and that's because the voting members are special government employees, and they have confidentiality agreements with FDA.

In terms of the application, for an MRTP, those we have to

post on the web for the public, and as soon as we get those, we start redacting the confidential information and posting those in waves for the public so that, you know, that they have that as soon as possible. And industry reps are -- will be able to see that as they are posted.

So I think the bottom line is, though, we try to get the public information out as soon as possible, as we did for this meeting. But we are required to get it out no later than 2 days before the meeting.

DR. HUANG: And they were draft questions, so we had an opportunity to provide input into that, is that correct, or --

MS. COHEN: So the questions that we post on the web are literally draft questions. And those should give you an idea of sort of the direction that we're going to.

The questions that you get today like these, we really try to make those as final as possible so that there does not need to be any editing during the meeting. So, you know, we really vet those a lot and try to make them very clear. On a rare occasion, if it's absolutely necessary, we might have to change those around. But, you know, we don't anticipate that.

DR. HUANG: Okay. Follow-up? Dr. McKinney, one more I

guess?

DR. McKINNEY: Just to follow up, and maybe I wasn't clear or specific, the company that submits the application, will they receive the questions? Because it's their application basically, and they probably want to think about the questions and be able to provide some feedback or present during the meeting. I understand industry, in general, but I'm really asking about the applicant.

MS. SUMMERS: Hi, I'm Karen Summers, and I work with Caryn Cohen on the Advisory Committee issues for the Office of Science.

And the applicant will receive a copy of the FDA background package approximately -- I think it's 18 days, 19 days, working days, ahead of the meeting. And that will include everything in the FDA package, including this draft version of the questions. And so they will receive it at that point. And then the Committee receives it like a day or two later than that because they can receive the unredacted information.

At the same time, the FDA starts the process of negotiating with the applicant on what should be redacted from the package before it is posted on the website. And any time

during that time, the industry reps are welcome to speak to the applicant and work out with them a way for the applicant to provide you a package early on if they're willing to do that and you're willing to do that.

But otherwise, you will get it the -- you know, when the public does, which for a product meeting is almost always 2 working days ahead of the meeting.

DR. HUANG: Dr. Wanke?

DR. WANKE: So do the TPSAC members, both voting and nonvoting members, have access to the full application or the redacted application?

MS. COHEN: Both voting and nonvoting members have access to the redacted application. Only voting members have access to the full, unredacted application.

DR. HUANG: Dr. Ossip?

DR. OSSIP: A million pages is staggering. I'm reminded of dealing with, say, doctoral students, a conversation I had with a historian colleague, where my approach is that if a student is using more than 25 pages to describe any particular study, they're using too many words. And my historian colleague sort of guffawed at that and said at 200 words -- at 200 pages, we historians are just beginning to clear our

throats.

So I'm wondering if the FDA sets any parameters around lengths of applications. And I ask that for two reasons.

One is because on the -- perhaps on the darker end, it could be a way to overwhelm a committee with just so much information that you kind of get lost in the shuffle of what's going on and may lower some standards for evaluation.

On the useful end, there may be things that would be important and really pertinent in the application to the applicant that would just get lost in that many pages. Not knowing the details of this application, perhaps it's perfectly appropriate, but it is harder to create a shorter application to be concise and organized and a presentation of information.

You know, we all have to do it with NIH applications, with manuscripts, with, you know, the kinds of things in our world that we do. And so I'm wondering if strategically there may be more of a win-win if it's possible to set some sort of parameters around length to make it a manageable process that in fact conveys the key issues the applicant wants to convey and that allows the Committee to do a fair review.

And I would expect there would be some, you know, some pretty broad limits because each application is likely to be

different, but the core question is are there any parameters that are set or FDA is considering setting?

DR. HOLMAN: So there are no limits on the size of an application. I guess a couple points, though, to keep in mind, a lot of information in an application are, for example, copies of manuscripts that they're citing from the scientific literature. There are datasets for any of the studies they've done. And as you know, some of those datasets can be quite large. And so a lot of information in some voluminous applications are, you know, supporting evidence, I guess.

The other thing, and this goes back to the timing question, by the time it comes to this Committee, FDA has gotten deep enough into a review that we're going to be able to pull out what we think are the most relevant pieces of information for the Committee to consider. We'll put that information in the background material you'd get ahead of the meeting.

In addition, we try during the presentations at the meeting itself to focus on what we think are the most relevant pieces of information. Similarly, the applicant does the same thing.

You are given access to the entire application because if

you want to go look at certain pieces or sections, we want to make it available so that you can see those sections. But I don't think the expectation that you should be putting on yourselves is to read a million-page application. But, again, it's just there so that you can go into the pieces or sections of it that you'd like to go into.

But regardless of the size of the application, we will do our best to try to summarize what we're seeing in the application, at least at that stage. And again, we're far enough in that we've had a chance to carefully go through the entire application, start to pull out what we think are the most significant issues.

We certainly haven't gotten to the point of making a decision or anything like that, but enough that we think we can provide you the information you need to make an informed decision. And that's the case no matter what the size of the application.

DR. HUANG: And so we don't scare away the new Committee members, I mean, yeah, I would -- you know, as Dr. Giovino mentioned, I mean, the staff and everyone -- FDA did a great job in the preparation materials. So it was digestible. I think they had really highlighted the key points, but we had

access to whatever we needed or wanted.

I think a suggestion to have the direct links to some of the cited studies would be good, but no, it was very -- I appreciate that preparation that was made for the Committee members. And so, yeah, don't feel like you have to read a million pages.

DR. OSSIP: And just so it's -- you know, thank you, and just seeing the pack that was sent out to the Committee, it was very impressive, and I appreciate the kind of boiling it down to its key areas.

But I was asking that, I guess, not just for the Committee, but for FDA to manage the volume of applications coming in because whoever does that initial read, whatever team does that, you know, it's a lot of paper to go through.

It is a different issue if the core text has some parameters around length or has a particular length, and everything else is in the appendix, you know, that the appendix can get quite long. But my question, I guess, was more about what goes in that core text of the application.

DR. HOLMAN: Yeah. And this issue you're raising is one that all the FDA centers have. I mean, there are applications across the FDA of all different sizes. And there are no strict

limitations per se because it's going to vary a lot depending on specifically what the product is in the application and what evidence the applicant thinks they need to provide to us.

And so it would be really difficult, I think, to set some sort of threshold at least at this point, you know, some sort of maximum size for a given application. But I hear your pointed concern, and I'm concerned about our resources just as much as you are.

DR. HUANG: Dr. McKinney?

DR. APELBERG: Sorry. Could I just add one more thing to that? I just wanted to add, for the MRTPAs, I mean, there's a unique aspect that Stephanie Redus mentioned that in the statutory requirements for submission, there's a requirement that applicant submit all the documents related to the health, you know, to the health risks of the product. And so that, you know, that requirement really requires applicants to provide all of the information that's relevant with respect to the products that are under review, so --

DR. HUANG: Okay. Dr. McKinney?

DR. McKINNEY: Thank you. We've talked about draft questions and the ability of the TPSAC to modify those questions. And as I was reading the transcript and looking at

the data that we received, I noticed that some of the questions were modified to the point where the applicant basically needed to provide data to prove a negative. So the question was modified.

And I know FDA, I know you guys are tight on resources, but you do review a lot of pages, and you come to areas, and you ask very specific questions where you think you need the TPSAC to comment. Can you guys speak to your thoughts about TPSAC modifying the questions? And is that helpful to you?

DR. HOLMAN: To an extent, yes, it's helpful. What this question really gets at is the tension we face with the timing because we have to make -- in the case of MRTPA, at least, we have to make the application, redacted version of the application publicly available. We need to get far enough into our reviews that we feel like we can provide TPSAC with a nice summary of what's in the application and what we think are the key parameters. But we also need to leave time for ourselves to finish our evaluation after the TPSAC, after we get the recommendations from the TPSAC, so that we can incorporate that into our evaluation. And so there is a real tension there with the timing of things.

And so that's really why I think sometimes the draft

questions -- you know, generally, I think they will look very similar, the final questions will look very similar to the draft. On occasion, because we're trying to get that information out quickly and have our TPSAC, you know, relatively quickly, there sometimes can be significant changes.

But as Caryn said, we put a lot of thought into these questions and what questions we think will be most useful to get the answers to in helping us to evaluate those applications. And so, you know, in general, I'd say, you know, we wouldn't anticipate a lot of edits coming directly from the Committee members on the questions.

That being said, I think if there are a number of questions or a question within our draft set that really are just extremely confusing, ambiguous, or you know, otherwise, you know, significant enough that you're not sure what you would do with them, I think we'd want to hear that so we could at least go back and think how do we capture the question that we were trying to capture because clearly we didn't convey it.

So I think to a limited extent, you know, we would be interested in getting some feedback because we want to make sure you guys understand what we're trying to get at. But at the same time, we're all scientists in the office, but we're

also regulators. And so we're very -- you know, we have legal and regulatory requirements, you know, or standards that we have to meet, and so that's why we're very careful about how we craft these questions.

And it may not be necessarily the way you might be thinking about framing it, but it's the way we need to frame it in light of what our regulatory requirements are, you know, the framework we have to ask these questions within. And so sometimes I think that's why sometimes the Committee can look at the question and go, well, I'd kind of like to say it this way. But we might actually need it stated the way we stated it because again that's our regulatory framework we have to be able to answer those questions within.

DR. McKINNEY: Can I follow-up?

DR. HUANG: Sure, Dr. McKinney.

DR. McKINNEY: Very briefly. Thank you for that.

My question, then, is when the TPSAC rewords the question and then they vote on the question, should that occur? Because you're very specific about your thoughtfulness into drafting the original question. Or should they vote on the original question or at least have some discussion and you go back and think about revising the question?

I just noticed -- I just -- that just seemed a little odd to me that they -- all right, we're going to rewrite the question and then vote on it. Just a thought.

DR. HOLMAN: So we'll be at the table when that conversation is going on. And, you know, I would -- we would be open to hearing how you guys might want to rewrite the question, and you know, we would provide feedback; yes, your rewrite sounds fine, that would still work for us, or no, really, that's not what we're getting at, can you just stick to the original question.

So, again, as long as we can talk it out, I think that's fine. But, again, we can get bogged down. You guys can get bogged down in rewriting a whole set of questions, and we want to avoid that as well. And so, in general, again, unless there's some major concern with the way we framed a question, my preference would be to answer the original question because, again, we've thought very carefully about how we framed it. And sometimes if you reframe it and give us an answer, that answer may not do us much good.

DR. HUANG: You have a question? No?

Okay. Any other comments? So any other comments regarding anticipating preparing for upcoming application

review for the TPSAC meetings?

(No response.)

DR. HUANG: Again, I think thorough overview of the materials that are provided.

All right. We'll move to Number 3: What information would be most useful to receive prior to an application review TPSAC meeting? Any additional comments on that? I think we've had support for what information was provided at the last one.

And yeah, Dr. Giovino?

DR. GIOVINO: This was kind of in what Swedish Match did, but I'm thinking about the harmful or potentially harmful constituents idea. And they talked about in regular smokeless, it's this, and in General snus, it's this, you know, it's much lower although -- so if there is a product that's heated, not burned, for example, I would love to see a set of graphs profiling as many of those HPHCs as possible in the referent product and in a referent product like Marlboro or some other combusted cigarette and in the potentially reduced exposure product.

I think that visual would be quite good. If a product is heated, not burned, it might be one profile. If a product is vaped, it might be another profile. But I think -- I mean, I

know that what's in there isn't necessarily what people get in and what they absorb, but it still would be a starting mechanism that I think the data wouldn't be that hard -- you know, I think the data could be gotten.

And I tend to think like a graphic like that would be useful. It would be to me, I know. Does that make sense to you, what I'm asking? Okay.

DR. HUANG: Yes, Dr. Thrasher?

DR. THRASHER: Yeah. I mean, I just wonder whether there's an effort to try and direct TPSAC Committee members' attention towards specific features of the application for which they have expertise that's relevant. And, you know, I guess we could all self-select into that process, but I wonder if that could be more purposeful or if it's done in a purposeful way.

DR. HUANG: Dr. O'Connor?

DR. O'CONNOR: Yeah, I was going to make a second point echoing what Dr. Thrasher just said, which is, you know, kind of like what we're used to in -- you're sort of given a application or a set of applications to review, and it might be helpful if, you know, for example, okay, you concentrate on this section or you concentrate on this section. And it might

help facilitate discussion a little bit better if we sort of divvied up parts of the application among the -- at least among the voting members.

And another point I was going to make as well is something that might be useful, whether it's even possible, but in the applications -- I'm thinking particularly of the consumer perception studies, where there may be raw data. If I'm looking through the application and say, oh, it would be really nice if they had done this analysis, could I feed that back to you and say you've got the raw data, could somebody there crunch these numbers for me and give an answer as to, you know, the question I'm asking; is it answerable in the data that they've provided?

DR. HUANG: I mean, the other thing I'd just reiterate, you know, the philosophy of the population effects and making sure there was adequate presentation of all of that material.

Any other comments on Question 3?

(No response.)

DR. HUANG: Moving on to Question 4: What information would likely be least useful prior to an application review TPSAC meeting?

Yes, Dr. McKinney?

DR. McKINNEY: So as I was looking at the material we were given, I was looking through the FDA kind of reviews of the literature, and I thought, well, this is pretty good as I was flipping through the pages. I think the first thing FDA did was made sure that the applicant thoroughly covered the literature in terms of the area, say, for example, epidemiology.

And then I looked at the methodologies of those papers and pointed out the deficiencies and where -- but when I went to the summary -- and this is just feedback -- I noticed that the conclusions were kind of based on some of the papers that had the most methodological deficiencies. And I thought, well, that's interesting.

So I guess I'm saying a bit more of a balanced kind of -- or is the purpose of the FDA just to summarize and say, here, TPSAC, this is kind of they did cover the literature, here are the methodological problems we saw with the literature, rather than providing a summary or kind of a conclusion? It's just a thought.

DR. APELBERG: I'll respond to that one.

DR. McKINNEY: Sure.

DR. ASHLEY: I've worked with these people a lot, and we

went through a lot of that. And clearly, as we were going through, we were going through, we were looking at the studies that were done, the methodology, the flaws, our concerns about that, and then we summarized, including the strengths and weaknesses of the reports.

And so as we went through that data, we definitely were -- we were not just spitting back to TPSAC just a list of studies and what we find. No. We were definitely including in that the strengths and weaknesses of those reports as part of our own analysis.

DR. HUANG: And I would say, I mean, I appreciate that because, I mean, if we disagree with that, we can do that, but I think having that interpretation/recommendation is also helpful.

Dr. McKinney?

DR. McKINNEY: So I agree with what you just said. I guess where I was going was, you know, there was a nice summary. And then there would be like two bullet points pointing to two specific papers that support like an adverse health risk. And when I went back and looked at the methodologies that were summarized in the presentations, those were the two papers that kind of had the serious method

problems. And that's all. That's all I'm pointing out.

But I think, overall, as I was going through the presentation, I was very impressed.

DR. HUANG: Dr. Fagan, did you have something or no?

DR. FAGAN: Yeah. I just wanted to add that I found those summaries extremely helpful, too. And that's part of what we had the opportunity to do after seeing all the presentations the first day, the majority of them, during that evening, having an opportunity to go back through some of the information and come back the next day with our own thoughts and opinions about what we saw. And so that's why I thought it was extremely helpful to have that information.

DR. HUANG: Okay. So we still didn't get much least useful, did we? Nothing? We're good?

Okay. Moving to Question 5: How would having only an Executive Summary or only the sections of the application that FDA planned to discuss, compared to having the entire application, impact your ability to prepare for an application review TPSAC meeting and give advice to FDA?

Dr. Giovino?

DR. GIOVINO: I guess I have a thought on that. Again, I think we would have access to the entire application obviously.

That's been stated.

I mean, we like details, you know? We're scientists. We're good with details. And Executive Summaries are clearly not detailed enough. They're nice to read, but they're not enough.

If FDA only wanted to discuss certain sections, it would be useful perhaps if FDA also provided an overview, a brief overview of the things that weren't to be discussed and maybe why they weren't relevant for the TPSAC meeting per se. But, again, I thought the level of detail at the last meeting was about right on, so --

DR. HUANG: Dr. Weitzman?

DR. WEITZMAN: I don't know that this is possible or if it's fair to industry, but an Executive Summary that had pointed the reviewers in the direction of where to look in the entire application if you wanted more information. I say that it may not be fair to industry because you've made a decision already and you're potentially influencing us in how we pursue your reasoning. But it certainly would be helpful to me to have a summary that says these are the parts of the application that are the most pertinent to this particular point. I don't know if other members would disagree.

DR. HUANG: I'm thinking that that was sort what was included in the briefing materials.

DR. ASHLEY: Yeah, that is what we will try to do. So we will try to -- what we'll do is there's certain questions we have to answer based on the statute. And actually, Ben had those questions, those four questions in his. So we will have those questions. And we will summarize our -- what we see in the application under each of those questions and try to explain to you what we're seeing in the application so that you can kind of reference that and look at that.

So I think we will be doing what you're asking for.

DR. HUANG: Dr. Fagan? Any other comments on this one?

(No response.)

DR. HUANG: Okay. And yeah, I'd echo what Dr. Giovino said. It was very appropriate, the level of detail, and having an Executive Summary or having some summary but then being able to access the details is important.

Okay. Moving on to Question 6, then: How was the information provided during the presentations at the 2015 meeting on the MRTPAs for the SMNA snus products helpful in providing advice to FDA?

Yeah, go ahead.

DR. FAGAN: After you --

DR. HUANG: I mean, I was going to say, I mean, the presentations really reinforced, allowed more further discussion regarding the briefing materials that we had, opportunity to pose questions regarding some of those issues that were brought out, and so I think they were a good complement to it and summaries, personally.

Yeah, Dr. Fagan?

DR. FAGAN: Yes. I'd just like to reemphasize that the 2-day format is really important because it allows the Committee the opportunity to think about what they saw on the first day. And so in terms of the presentations, having that format in the way in which it was done, I thought, was extremely helpful.

DR. HUANG: Any other comments on 6? Oh, Dr. McKinney?

DR. McKINNEY: Were those presentations provided prior to the meeting? And then my question is, would it be helpful to have those presentations prior to the meeting, and is that possible?

DR. HOLMAN: Well, they are really meant to complement the background material. And so I'm not sure there's that much utility -- I mean, that just gives more reading material for

you guys. That's going to be redundant with the reading material we've already given you. And so --

DR. McKINNEY: It's the same thing --

DR. HOLMAN: Yeah, really, it's the same thing. So, you know, but we do think it's important to walk through it on Day 1 to make sure because it is a lot of material you guys are getting through. We realize you have day jobs, and this isn't your day job, and so we do think it's important, though, to walk through those. But, again, I don't necessarily think there's a lot of advantages to you to get those presentations ahead of time.

DR. HUANG: Yeah. And probably thinking back on that, that's probably appropriate because it does, yeah, reinforce what we've already received in the other background materials, but just sort of summarize and opportunity for more interaction.

Any other comments on 6?

(No response.)

DR. HUANG: Question 7: What information would be useful as part of the meeting presentations during an application review TPSAC meeting?

Yes, Dr. Ossip?

DR. OSSIP: One thing that I found really helpful in the materials that you sent, and this was in the briefing document from the April 2015 meeting, were the MRTP criteria that were on pages 8 to 10. And I believe that was repeated in one or more of the presentations today.

And I think maybe particularly for the newer members, it might be helpful if we could have a hard copy of that just to keep in front of us to keep us oriented and focused on what the criteria are during the meeting.

DR. HUANG: Any other questions? Yes, Dr. O'Connor?

DR. O'CONNOR: Yeah. And to the extent possible, having the presentations aligned in some way with the questions. So in the terms of the background questions -- or in terms of the background presentations, and then -- so that there's a more clear link between the information that's being summarized and the questions we're meant to answer later on.

DR. HUANG: All right, Question 8: What information would not be useful as part of the meeting presentations during an application review TPSAC meeting?

(No response.)

DR. HUANG: I mean, certainly the obvious is extraneous sort of information, but --

DR. ASHLEY: We were just trying to give you guys a chance to say I really don't need to hear about that, so it's okay.

DR. HUANG: Okay. Oh, our last question: How might the TPSAC meeting be structured so that the Committee is best positioned to provide advice to FDA?

Dr. O'Connor?

DR. O'CONNOR: Yeah, I think, yeah, in thinking about the last meeting and -- I think it was helpful to have a day that was devoted to the application and sort of the applicant presenting their summary of the application and FDA providing its initial assessment. We can go home, think about it, and then we start really getting into the questions on a second day. And, you know, potentially depending on the nature of a particular application, but we might need 2 days to talk about it after hearing about it. But that's probably going to vary from application to application.

DR. HUANG: Dr. Ashley?

DR. ASHLEY: Let me just ask a question because I'm anticipating the possibility -- it's not -- it wasn't in the case we had before, but there is the possibility later on we may have multiple applications to have to go through. And so there are a couple ways to try to do that and just want to get

your opinions on that.

One way would be to -- let's say we only -- because we have so many applications, we only have one day for each application. One would be to start in the morning, do the application, and then have the questions and everything in the afternoon, and then the next day, go to another application.

Another alternative would be to start one application in the afternoon, let you think about it overnight, and then ask the questions in the morning, then start on a new application in the afternoon. I don't know which would be easier for you or better.

DR. HUANG: Yeah. Dr. O'Connor?

DR. O'CONNOR: I guess it depends on how different those applications are. So I could say if they were sort of, you know, apples falling from the same tree and the basic background information is similar, then I could see that sort of a setup working. But if you've got application 1 is in this product class and application 2 is in a totally different product class and very little overlap in terms of the underlying research questions and things like that, I think that would be really hard to deal with.

DR. HUANG: Dr. Fagan?

DR. FAGAN: Yeah. I'll just restate what I mentioned earlier is that having that evening to digest it -- I mean, these are really critical recommendations that we're making, and I don't want us to rush and make recommendations for the sake of trying to fit two applications in one day. So having that evening to think about things, reflect on it, you know, look up a few more papers, I just found it extremely helpful, so --

DR. HUANG: Yeah. I'd agree also. I mean, it would be, then, a shame to get everything done in one day and not have a chance to revisit it after having had that time to digest some of the information in the discussion. And maybe as there's more experience with multiple applications, then people will -- I'm sure there will become more speed or familiarity.

But other comments?

Yes, Dr. McKinney?

DR. McKINNEY: Thanks for that clarification. And I thought my comment would be related to the question, but based on your clarification, it's not. But that's okay. I'm going to make it anyway.

As I think about what Dr. Giovino said, which is we're scientists and we like details, I just want to reiterate and

support what Dr. Ossip said in terms of having the criteria for an MRTP so that we don't necessarily -- so that we keep our eye on the big picture, so that should always be part of the meeting.

DR. HUANG: Any other comments?

Yes, Dr. Ossip?

DR. OSSIP: So sorry, but some of us are going to need to start peeling off at 2:30 to get to our flights on time, so I just wanted to ask if there are any things that you or the FDA really want to have, make sure that you get in while the full Committee is here, while we still have a little bit of time?

DR. HUANG: This is the last question, so they've got everything. We got through it before 2:30.

Anything else? Yeah, any other critical -- yes, Dr. Ossip?

DR. OSSIP: Just thank you so much to the FDA for doing this. I think as a new member of this Committee, this has been enormously helpful and, I think, will really enhance the productivity of subsequent meetings having been through this experience and the quality of the presentations and the thought that went into putting this together to bring us up to speed.

DR. HUANG: I agree totally.

Other comments?

(No response.)

DR. HUANG: All right. Well, people, the weather looks -- I guess is it clearing? I don't know, but got a 2:30 departure, so if there's nothing else, then I think we're adjourned.

Thank you all very much.

(Whereupon, at 2:30 p.m., the meeting was concluded.)

C E R T I F I C A T E

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

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

April 6, 2017

Silver Spring, Maryland

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

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