UNITED STATES FOOD AND DRUG ADMINISTRATION

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DEEMED TOBACCO PRODUCT APPLICATIONS:
A PUBLIC MEETING

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TUESDAY
OCTOBER 29, 2019

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The public meeting was held at the FDA White Oak Campus, Great Room, Salon A, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:30 a.m., Todd Cecil, Moderator, presiding.

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

8:33 a.m.

DR. CECIL: We aren't quite as full as we'd like to be. I imagine we will see a lot more people showing up in a few minutes. Coming through security is a little bit difficult as I'm sure you all know.

We will expect this to be a fairly full room. We apologize for the size of the room. This is what was available to us when we booked the room, and so get to know your neighbors and enjoy the interactions.

I want to say welcome to the second day of the Fall Technical Forum. That was a name I just made up by the way, so you should all understand that.

My name is Todd Cecil. I'm the Associate Director of the Division of Product Science. I misquoted myself last year and called myself from a different division, so I had to make sure to get it correct this time.

So, I get the chore of talking to you

about logistics and letting you know that the restrooms, if you did not already know, are out the doors this way to your right and around the corner.

For those who have not already done so, bag lunches are available for purchase from the little kiosk right over here. You can get the forms since we had FDA -- forms, and right at the desk out front, and you can take that over and they'll go ahead and deliver those before the lunch is available or lunchtime appears.

Let's see, we will have one lunch break for about an hour, and I'll let you know how long it will be or when it will start. We'll have two breaks throughout the day as well, one in the morning and one in the afternoon. The agenda that you were given does not show an afternoon break, however we will have a break between the two panel discussions just to give us time to get everybody rearranged. All right.

So, for those who were not present as we began yesterday, Anne did a great job in

introducing the goal of the meeting and Matt did a great service as well. So let me repeat some of the words that they stated. Rather than make it up, I will read it.

This meeting intends to provide information to the Agency's expectations for tobacco product applications with a particular focus on deemed tobacco products.

One of the goals is to continue to increase transparency in advance of the court-mandated submission deadline of May 2020, by only giving more information on application processes, but also by presenting review perspectives and lessons learned in the evaluation of the applications that we have reviewed up to this point.

We do not intend to discuss anything that's outside the scope of the meetings. Things like any pending decisions or litigation, any future rulemaking, THC, enforcement discretion policies for deemed products, and pulmonary illness for e-cigarettes.

I do also want to point out that we will be taking questions for panels only. We'll not be asking questions of the individual speakers.

If you're in the room, there are 3 by 5 cards that are being handed out. If you need one, just raise your hand. Once you have filled out that card, because it's going to be such a full room we hope, hold your hand up a little higher so that the people can see that you have a finished question you'd like to hand up to the moderator.

For those of you online, if you are interested in engaging, we are available at workshop.ctpos@fda.hhs.gov. I do want to ask the folks online, and there's quite a few of you online, to please send your questions in.

The folks in the room actually had a great many more questions yesterday than those of you online, and there's a lot more of you online. So we're hoping to get a lot more comments online today, especially since today we're going to be

talking about the scientific aspects of the PMTA and the SE pathways.

We started yesterday with a couple of talks on the premarket pathway for PMTAs for scientific content. Ouida Holmes and Priscilla and Christina Saba spoke. Hopefully, you recall those presentations and you will have questions. I'm sure many questions have been submitted and we will give those to the panelists at the appropriate time.

So we'll begin today with the first presentation which is Lessons Learned from the PMTA Review by Hans Rosenfeldt. I'll turn it over to you Hans. Thank you.

DR. ROSENFELDT: So good morning. My name is -- Hans Rosenfeldt. I'm the Deputy Director of the Division of Nonclinical Science. And I will talk to you this morning about Lessons Learned from PMTA Reviews. How do you advance? Got it. No --

So, FDA's goal in product regulation is to reduce the public health risk and

individual health risk to the user posed by tobacco products available on the U.S. market.

For the premarket tobacco product application or PMTA pathway, achieving this goal involves the determination of whether the new product described in such a submission is appropriate for the protection of the public health or APPH.

So you may have heard this abbreviation, APPH, yesterday. I'll be using this abbreviation throughout my talk. So this designation, appropriate for the protection of the public health, is per the Food, Drug and Cosmetic Act as amended by the Tobacco Control Act of 2009.

So, as reflected in the draft NPRM on PMTAs, which is currently open for public comment, it is proposed that many different lines of evidence can support the determination whether a new product submitted under the PMTA pathway is appropriate for the production of the public health.

And such a determination is proposed to be, to use several different lines of evidence, including consumer understanding and perception, overall population health risk, individual health risk, abuse liability, and effect on vulnerable populations.

Each of these different lines of evidence may themselves be composed of different kinds of scientific information from published literature or submitted original studies.

So for example, overall population health risk would include information on population models, user behavior studies, epidemiology studies. And, for example, individual health risk evidence would include information on product manufacturing and distribution; information on toxicology studies, clinical studies, HPHCs and so forth.

And for consumer understanding and perception, likelihood of use studies, comprehension and perception studies would fall in that category.

Behavioral pharmacology and abuse liability information would include studies on nicotine content, nicotine metabolite, and work on subjective effects of nicotine.

And finally, information on the effect of a tobacco product on vulnerable populations would include how the product affects the health risks of consumer perception abuse liability in groups such as pregnant women, children, youth and young adults. It's important to note that the affected vulnerable population would depend on the product.

So, as reflected in the NPRM on PMTAs, which is currently open for public comment, FDA's goal in product regulation, as I mentioned before, is to reduce the public health risk and individual health risk to the user posed by the tobacco products of the products available on the market. I would add to that that non-users are also very important in this regulation.

Thus, the evaluation of both risk to the overall public health and to individual

health is a component of FDA's evaluation of PMTAs. This evaluation includes a health risk comparison between the new product and products that users of the new product would likely use if the new product were not marketed.

Importantly, all actions under the FD -- the Food, Drug and Cosmetic Act, are also governed by the National Environmental Policy Act, or NEPA, which requires that all actions have an associated environmental assessment or EA, or categorical exclusion.

FDA has accumulated some lessons stemming from the review of PMTAs and PMTA meeting request submission materials. FDA would like to share these lessons with you in this presentation.

Most of these issues affect the comparison of the new product in a PMTA to comparative products on the U.S. market and involve review issues important in determining whether marketing of a new product is appropriate for the protection of the public health.

One additional issue that can delay a positive action or cause a negative action is the lack of an adequate EA or a qualified claim of categorical exclusion in this submission. More on this issue later in the presentation.

So, I'd like to first focus on the importance of identifying the user in tobacco product risk comparisons of PMTA. So you may have seen this slide before, and I put this here for a reason because all the lines of evidence that you would think of in terms of the APPH determination, can also be looked at from the point of view of the user.

So for each product, the relative importance of each of these lines of evidence can vary depending on the user population. So for example, the user, who the user is, can affect consumer understanding and perception. It can also affect overall population health risk or individual health risk. It can also affect abuse liability and the effect on vulnerable populations.

So, it's useful to consider the health risks of products that are both within the same category as well as those that are in different categories. The focus of health risk evaluation of a new product will take into account who the likely user of the new product is.

Users of the new product are key because the health risk evaluation needs to occur from their point of view. For example, if users of a new product in a PMTA are not likely to use combusted cigarettes for example, then the health risks of combusted cigarettes are less relevant to users of the new product because they're not likely to be exposed to combusted cigarettes.

So one central issue in PMTA review is identifying which comparative tobacco products would be used by users of the new product under review if the new product is not authorized to go on the market.

These tobacco products represent the most relevant comparators for the new product, especially in the context of assessing the health

risk posed by the new product. The user population can determine the health risk comparisons that are most appropriate for a new product under PMTA.

Non-users are also important to the overall APPH evaluation. While users are at greater risk of tobacco-related disease, and while this necessitates a focus on users for individual health risk determinations, the non-users are also important because of important issues such as the potential for initiation.

Tobacco products can be organized along a continuum of risk as depicted below. Currently, the majority of tobacco products sold in the United States cluster along the higher end of the spectrum, combusted cigarettes.

However, comparing the potential health risk of a new product in a PMTA to combusted cigarettes is not always appropriate as I mentioned in the previous example. For example, if users are not using cigarettes.

Another scenario in which the identity

of the user of the new product affects risk comparisons may include if the likeliest user of the new product is likely to be a user of a tobacco product that is not a cigarette, such as an oral tobacco product. The health risk posed by the similar non-cigarette products may be compared to the health risk of a new product in the evaluation of a PMTA. In all cases, the effects of non-users on non-users are important considerations that need to be assessed.

An additional scenario in which the health comparison to more than one product category could be useful follows. In the case of a new cigarette product with very low HPHC deliveries relative to similar products in the market, but a low switch rate from conventional cigarettes.

That is, most smokers are not using this product, but the product itself has very low HPHCs, it could be argued that there is a large drop in individual health risks for the small number of smokers switching to this hypothetical

very low HPHC-level product.

There would be, in addition, a drop in health risk for the large number of users of the same class of tobacco products who would switch to the same hypothetical very low HPHC-level product which would result in an overall health benefit to the population.

Therefore, a comparison of the new product to conventional cigarettes in addition to products on the U.S. market -- similar products to the low-level HPHC product on the market is relevant. Potential effects on non-users are also relevant and would be taken into account.

In some situations, likely users of the new product may be members of vulnerable populations. These vulnerable populations include the youth, under-served rural populations, pregnant women, et cetera.

These users may bear disproportionate burden of tobacco-related disease. They may have disproportionate use patterns and exposures. And these populations, as appropriate, may be

considered in the overall APPH evaluation.

A disproportionate effect on these populations can affect the APPH determination even if they're a minority of likely users, and I would add even if they are non-users.

So here are some hypothetical examples. So, for a new product that is hypothetically an ENDS, if the user product data indicate that there's a large number of users who would switch from conventional cigarettes, then conventional cigarettes might be a useful comparator. In such cases, the effects on non-users would also be looked at.

In the case of an ENDS product where there's a large number of users who will switch from other ENDS products, then it could be argued that another ENDS product or other ENDS products on the market would be a useful comparator. Again, the effects on non-users would be addressed.

In the case of a smokeless tobacco product where only a minority of users switch

from conventional cigarettes, however there is a chemical analysis indicating that there are very low HPHC deliveries. In that case, it may make sense that conventional cigarettes and smokeless tobacco products are useful comparators.

I would add that in the case of -- even though it's not there -- the effects on non-users would always be taken into account in the glass cases of the smokeless tobacco product.

So onto product characterization. So the following parameters are useful for FDA to define a new product sufficiently under the PMTA so that the new product can be compared to relevant products on the U.S. market, manufacturing processes, manufacturing controls including controls on HPHCs, complete ingredient information, analytical data including HPHC data, and stability information.

Product characterization and control is important to the comparison of a new product to comparative products. For example, if a new product is manufactured in such a way that HPHC

deliveries are not consistent over time, it is very difficult to evaluate the health risk of a new product relative to comparative products.

Product characterization also provides important information that the FDA needs to determine that there are no ingredients or degradence of concern in the new product. For example, inclusion of toxic additives, stability problems, and potential presence of toxic leachables are all issues that could affect the health risk evaluation of a new product.

Without good new characterization, FDA cannot establish whether the product can be manufactured consistently over time that the HPHC profile assessed in the PMTA application is relevant to the HPHC profile of the product as it is manufactured in the future.

So the question is, okay, so what is the comparison today to the product, but what will be the comparison tomorrow. Is the set of HPHCs and the set of health risks posed by the product today, will it remain consistent over

time or will it not?

So, and then additionally, good product characterization will allow the FDA to understand whether the product will remain stable and not pose further health risk during its shelf-life.

So, on to Bridging Data. There are two main kinds of data bridging that we've encountered. When data generated using a product that is not the new product under review is applied to the evaluation of the new product, and when data generated from the study from one population is applied to the evaluation of another population.

So as reflected in the draft MPRM for PMTAs, which is currently open for public comment, in order for bridge data generated with one product -- sorry -- in order to bridge data generated with one product so that it can apply to the evaluation of another product, applicants would need to show that results from studies of a new product that is not the new product under

review, are applicable to the evaluation of the new product.

Without this justification, the submitted data generated with any products, other products, products other than the new product, is of very limited use to the evaluation of the new product listed in the PMTA.

So, types of studies using test articles that are not the new product under review may include studies of product prototypes, studies with products that have similar characteristics to those of the new product under review and published studies from the scientific literature.

The kinds of information that these studies could include, include clinical information including biomarkers of exposure and harm; nonclinical information including in silico, in vitro, in vivo, ex vivo toxicology studies; analytical information including HPHCs and the data on HPHC delivery.

So this is a very busy slide so I'm

just going to touch on a couple of these examples. So applicable examples include, for example, toxicology of studies using a prototype product submitted in support of a new product.

In such a case, it would be useful to include a strong rationale explaining --- sorry -- including in such a situation, it would be useful to include a strong rationale explaining how results are relevant to the new product. An HPHC comparison between the new product and the prototype product; an ingredient listing between prototype product and new product.

And then, for example, another example would be clinical studies using biomarkers of exposure and biomarkers of harm using a test article different from the new product.

In such a case, it would be useful to include a strong rationale explaining how results are relative to the new product; an HPHC comparison between the new product and the prototype or the different product; and an ingredient listing between the two products. The

one that is supposed to replace the new product.

For any prototypes used in studies submitted in support of a new PMTA -- new product in a PMTA, the following items are useful.

That the prototype be clearly named and identified; that the prototype be distinguishable from other products referenced in the application including the new product under review; that the prototype be characterized in such a way that submitted studies allow for conclusions about the new product; and a rationale indicating why data generated using the prototype can be applied to the evaluation of the new product.

Inclusion of data generated using prototypes without clear identification of the prototypes and without a rationale for why this data applies to the evaluation of the new product is a common problem in PMTA review.

Bridging can also occur when data from the results of one study population is applied to another population. This kind of bridging can

happen with social science, epidemiological data, and clinical studies.

In such cases, a rationale explaining how data generated from the study of one population can be applied to the population of interest is useful. Important considerations include the demographic comparison of the two populations and the use pattern comparison of the two populations.

For example, data from a population that has a high prevalence of ENDS use is best compared to another population that also has a high prevalence of ENDS use.

So, on to product use patterns. A clear description of product use patterns is very useful to establish two very important questions. One, who will be exposed to the new product. And two, how much exposure to the new product will occur and in what context.

It is generally helpful if the results of product use patterns and likelihood of use studies aligned with the selection of the

comparative products used in the health risk comparison of the new product to the tobacco market.

Product use data can provide important information that can determine whether users of one class, for example cigarettes, are likely to switch to a new product of another class, for example ENDS; provide information on the youth appeal and the risk of initiation; provide information on the likelihood of dual use; provide information of human exposure that can be useful for interpretation of toxicology studies; provide data that can be used as inputs for population models that estimate net public benefit or harm.

As such, product use patterns provide very useful information for the overall evaluation of the new product. In a useful study, endpoints match the effect that they are intended to address.

For example, if the intent is to measure likelihood of use, a study that measures

likelihood of use and provides a direct quantitative measure of likelihood of use is most informative.

If a study with an endpoint other than likelihood of use is submitted, it would be helpful to provide explanation for why study endpoints were chosen and how they were validated.

So, on to marketing and advertising. So submitted advertising -- it would be helpful for submitted advertising to reflect the advertising that will be used if the new products are authorized under PMTA.

Challenging situations can crop up in the case of a parallel PMTA and MRTPA submissions in which advertising with MRTPA language is submitted with a PMTA. For example, the inclusion of modified risk information in advertising materials used in likelihood of use studies that are submitted to both MRTPA and PMTA submissions is problematic for the PMTA.

PMTA reviewers cannot consider results

generated with advertising containing modified risk claims.

On to environmental assessments. So the need for an environmental assessment or qualified claim of categorical exclusion for each application is not tied to the APPH determination. Instead, an EA is necessary pursuant to the National Environmental Policy Act or NEPA under 21 CFR which states that all applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion.

NEPA requires the preparation of an EA for FDA to proceed with the marketing order for a new product under the PMTA pathway. Lack of an EA is a common reason for PMTA applications not moving forward to scientific review.

So what is an EA? An EA is a stand-alone document for the public to understand the government's environmental considerations. The regulations for an EA can be found under 21 CFR, and a recommended outline of an EA includes a

cover page, a table of contents, the body of the EA, and any appendices, including confidential appendices, that include proprietary marketing information. FDA recommends that each EA focus on only one product.

So recommendations for inclusion in the body of an EA include applicant and manufacturer information; product information; the need for the proposed action; alternatives to the proposed action; affected environment; potential environmental impact; alternatives including manufacturing, use and disposal alternatives; lists of preparers; list of agencies consulted and references.

It's recommended that an EA include discussion on the following topics: air quality, water resources, soil, land use and zoning, biological resources, solid waste and hazardous materials, flood plains, wetlands and coastal zones, regulatory compliance, socioeconomics and environmental justice, and cumulative impacts.

So, example potential impacts of

tobacco products may include impacts resulting from manufacturing of the new product; impacts resulting from tobacco cultivation; nicotine extraction; synthetic nicotine production; second-hand and third-hand exposure from use; hazardous waste from disposal of ENDS components and batteries, et cetera.

The FDA would like to emphasize that confidential business information can be included in confidential appendices. So according to 21 CFR, confidential business information should be summarized and included in the EA to the extent possible. The EA is a stand-alone and public document and the confidential appendices will remain undisclosed.

So in conclusion, as reflected in the draft notice of public rulemaking on PMTAs, which is currently open for public comment, many different lines of evidence can support whether a new product submitted under the PMTA pathway is appropriate for the protection of public health, including an individual health risk comparison,

an overall population health risk comparison, an assessment of consumer understanding and perception, an assessment of abuse liability, and an assessment of the effects on all number of populations.

It's very important to compare the health risk of a new product to comparative products that are likely to be consumed by users of the new product.

Product characterization and manufacturing controls are very useful to the comparison of a new product to comparative products. Health risk evaluations cannot be made without the proper characterization of the new product.

For bridging between products, as reflected in the draft NPRM, its useful information includes a rationale for why results from studies of a product that is not the new product under review are applicable to the evaluation of the new product.

Product use patterns are useful in

addressing two questions: who will be exposed to the new product, and how much exposure to the new product will occur and in what context.

And then finally, NEPA requires at least the inclusion of an EA in each PMTA for FDA to proceed with a marketing order for a new product under this pathway. Lack of an EA is a major reason for PMTAs not moving forward to scientific review. Thank you very much.

(Applause.)

DR. CECIL: Thank you, Hans. It is now time for us to transition to the panel discussion. Can I invite all of our panelists to come up to the table.

While they're coming up, I did also want to take this moment to remind everyone that the slides that are being presented, as well as the recording and the transcripts will be made available on the FDA website in 30 to 60 days. Probably closer to 30, but we don't -- it all depends on getting all the materials available.

All right. This is a large panel. We

have a number of questions and we have plenty of time. We're a little ahead of schedule, thank you, Hans. It will give us more time for answering your questions.

We also want to ask each of our panelists from outside the FDA to keep their remarks to five minutes or less, but we do invite you to make opening comments. So may I turn it over to Jason?

DR. FLORA: Good morning and thank you for this opportunity to discuss the PMTA pathway. I'm Jason Flora and I lead Regulatory Affairs Scientific Integration for Philip Morris USA with a focus on regulatory requirements for potentially reduced harm products.

Over the last two days it's been helpful to hear details on FDA's proposed PMTA rule and the scientific content to support an application.

The PMTA pathway creates an opportunity for manufacturers to provide science and evidence to demonstrate that a new tobacco

product is appropriate for the protection of public health.

In the development of innovative products which could potentially reduce the harms of combustible tobacco use requires a thorough but achievable pathway. The proposed PMTA rule is a good step, and we look forward to submitting our detailed comments.

Today, I'd like to talk briefly about what happens after market authorization; how we should address improvements to products that have received market orders through this extensive PMTA process. Manufacturers will likely need to make product improvements after receiving marketing orders.

We will continue to learn about these products or how these products are used once they're in the marketplace, and manufacturers should have the flexibility to make the necessary product improvements. Improvements to authorized new tobacco products will continue to advance tobacco harm reduction.

These could include enhancements that accelerate the complete switching from a traditional tobacco product like cigarettes to new, potentially reduced-risk products.

They could address consumer complaints such as product quality or durability. They could improve manufacturing efficiencies or establish supplier security, ultimately allowing these products to reach more adult tobacco consumers. And they could also include technologies that prevent youth access to these products, because tobacco products are for adults only.

We are encouraged by the fact that FDA has recognized a supplemental PMTA process in the proposed rule. FDA clearly recognizes the need for a streamlined process for product improvements that increases the efficiency of submissions by the applicants and reviews by FDA.

While the supplemental PMTA process described in the proposed rule is a great step, I'd like to address a few important points.

First of all, improvements to authorized tobacco products will vary greatly in scale as will the scientific evidence needed to show the impact of the change. So the supplemental PMTA process should not be a one-size-fits-all. Some modifications will be very minor, while others will be more complex.

Both the scientific evidence provided by the applicant and review times conducted by FDA should be proportional to the scale of the product change. The proposed rule suggests that the supplemental PMTAs are on the same 180-day review timeline as new PMTAs.

However, some minor modifications to authorized products could require minimal to no scientific studies, and thus require minimal review time. For example, changes that would not affect emissions such as changes in connection type or thread type of any vapor product.

A potentially more significant change is a minor change in draw resistance. This could affect emissions which would require more

scientific data in the supplemental PMTA and thus need longer review times.

But in either case, a review of a supplemental PMTA should be much less substantial than that of a new PMTA due both to the scope of the change and the efficiencies of cross-referencing studies previously evaluated in the original PMTA.

FDA has embraced least burdensome approaches in other centers within the agency. Those pathways have well-defined criteria and specific review times, principles CTP should consider.

So the second point I'd like to make is that manufacturers should have clarity regarding where on the spectrum a specific change falls and competence on how to proceed.

As stated in the proposed rule, supplemental PMTA is available only to modifications that require submissions of limited information and is prohibited where the supplemental PMTA format would be confusing,

cumbersome, or otherwise inefficient while these are subjective qualifiers which will present challenges to manufacturers attempting to determine if they can proceed with the supplemental PMTA for product improvements.

Without better clarity on this issue, manufacturers will need to make submissions on trial-and-error basis, have numerous meetings with CTP which could delay the opportunity for improved potentially reduced risk products to reach adult tobacco consumers. Supplemental PMTA should be clearly defined and streamline pathway for product improvements.

So finally, we're talking about improvements to products that FDA has already determined to be appropriate for the protection of public health. I would hope that there would be alignment among stakeholders in supporting timely and predictable review of supplemental PMTAs.

So we look forward to listening and learning in this meeting and providing our

perspective in the comments on the proposed PMTA rule. Thank you.

DR. CECIL: Thank you. Elaine?

DR. ROUND: Good morning. My name is Elaine Round. I'm a Senior Director in Scientific and Regulatory Affairs at RAI Services Company. And RAI Services Company is responsible for FDA submissions on behalf of Reynolds American operating companies including R.J. Reynolds Tobacco Company, American Snuff Company, Santa Fe Natural Tobacco Company, and R.J. Reynolds Vapor Company.

First, I would like to thank the Agency for hosting this workshop and inviting others to sit around the table with them. These workshops are a great opportunity for us to learn about FDA's current thinking, and I certainly appreciate FDA's interest in the applicants' perspective as well.

As you heard from my colleague Dr. Campbell yesterday, we submitted our first PMTA just a couple of weeks ago. Putting these

applications together is complex, even when the expectations for content are fixed and understood.

However, those have continued to evolve even over the last several months. The final ENDS PMTA guidance published in June added new recommended constituents for analysis in aerosol. And then the proposed rule published in September provided more clarity around what are likely to be the Agency's expectations for PMTAs.

The information is welcomed and is needed, but the timing is extremely challenging given the public pressure from the FDA Commissioner and others to submit applications as soon as possible and given the current May 2020 submission deadline for products in market.

Ideally, the discussion of content would be one unencumbered by the urgent consideration of timing needed to conduct the studies and finalize the applications. However, any changes to the expected content must include the context of what is possible given the current

deadline.

So with regard to specific scientific content, I'll focus my remarks on two specific topics. The first is bridging.

Bridging is arguably one of the most important parts of any deemed product PMTA for several reasons. The moving submission deadline has made it difficult to plan for studies for a complete application.

All applicants have limited resources available to them to conduct studies and we all rely on the same contract labs and research organizations to gain data, and many applicants have multiple products for which to submit PMTAs.

And that's the case because these products are the world's best attempt so far to provide smokers with satisfying alternatives to combustible cigarettes that virtually all agree are far lower on the risk continuum.

Bridging helps maximize the utility of studies to increase product options. And that's important because we know there is no single one

right solution for every smoker who wants to switch down the risk continuum.

And the preamble to the proposed rule, FDA has provided its most detailed guidance on bridging to date, and I certainly appreciate Dr. Rosenfeldt's comments in the last presentation.

However, I am not aware of any solid examples of where FDA has accepted bridging in a cleared application to date, so I would ask FDA if they are willing to share such an example. I'd be very interested in understanding that.

And in the examples shown by Dr. Rosenfeldt, all of them recommended the inclusion of engineering specs or ingredient listings which suggest that an applicant can only bridge to a product that they manufacture. So I'd also ask FDA if that's their intent.

Second, I'd like to address FDA's expectation of actual use studies. And FDA is defining those studies of how consumers actually use the product in a simulated use setting or in a real world environment. And these studies

would include topography, frequency of use and use trends over time.

The proposed rule indicates that FDA is considering this as a possible requirement for PMTAs. And given the precedent set for multi-week actual use studies in cleared PMTAs to date, I'd argue that this is a very tall order and particularly so for products that are not yet in market.

The resource requirements for this type of study can be astronomical depending on the number of products to be included, and may not be actionable for smaller manufacturers in particular.

I'd encourage FDA to consider that these studies can't be conducted under real world conditions if a product is not yet marketed. And true real world use information can and will be gathered in post-market data which will be the ultimate test of whether a product is appropriate for the protection of the public health.

And FDA is also proposing that abuse

liability studies and likelihood of use studies also be required for PMTAs, and those would inform on the likelihood of product use prior to marketing of the product without the need for actual use studies.

So, I'd like to end by emphasizing that clarity around the information that we're discussing over these two days is not only important to those of us in the room and those tuning in, but also it's important to, and possibly more important to the millions of smokers who already use many of these deemed products to continue not smoking combustible cigarettes, as well as the millions more current smokers that would use them if given timely and appropriate regulatory clearance.

It would be a shame if this process breaks down in such a way that smokers no longer had access to the products that have helped or could help them switch to a product lower on the risk continuum. So I believe it's in everyone's best interest to ensure that the process in

addition to the products are appropriate for the protection of public health.

DR. CECIL: Thank you, Elaine. Steve?

MR. SEIFERHELD: Good morning. My name is Steve Seiferheld, and my expertise lies in the field of Consumer Research and Insights. Today I'm attending on behalf of Venebio, a life sciences consulting firm that specializes in projects complex in nature typically inclusive of data analytics, regulatory submissions, scientific writing and more.

From 2016 through April of this year, I was employed at Swedish Match as the Director of Market Research where I led all consumer research included in the amended MRTP application for General Snus, which on October 22nd was announced as the first product to be granted MRTP. I'd like to congratulate my former colleagues either in attendance or tuning in today, as well as FDA, on achieving that milestone.

There is no doubt as to the paramount

importance of scientifically robust consumer research needed for PMTA. That's been discussed under the FD&C Act that the finding of whether a product would be marketed as appropriate for public health explicitly considers consumer behavior and intentions, and in fact, fundamentally, the definition is reliant on consumer data.

I observe with interest how some manufacturers attempt to satisfy their arguments using publicly available data and surrogates to direct consumer feedback. Ultimately, your PMTA is at best shaky without data that connects to your category, brand and variety.

The FDA's proposed rule for PMTAs makes numerous references to required and/or recommended inclusions that rely directly on consumer research, touching on things such as marketing, initiation, cessation, label, labeling advertising, and label comprehension.

So anecdotally, I can cite numerous conversations with manufacturers during which

they cite lack of clarity and direction from FDA on what needs to be included in the PMTA. However, in my opinion with regard to consumer research, I think FDA has provided significant clarity.

A thorough review of publicly related documents, including information from the MRTP applications on General Snus, Camel Snus, IQOS, 22nd Century and Copenhagen reveals significant insight into what FDA expects from consumer research in terms of study design, sampling, data analysis and reporting.

The proposed rule and the PMTA guidance lay out a very reasonable framework for the expectation. From there, one needs to think creatively about where else to find appropriate, methodological ideas.

I have found useful an array of FDA documents more directly related to healthcare, including information meant to focus on over-the-counter medications and patient-driven pharmaceutical research, being mindful that CTP,

while facing some unique challenges, is in fact part of FDA.

It follows that guidance given to healthcare companies could reasonably apply to PMTA, especially on topics related to statistical science and consumer behavior. In situations where FDA has failed to provide more specific guidance on how to proceed, I believe inexperience of all parties to be the most significant contributor.

And I would invite people to think back if you've ever been part of a Master's thesis or a dissertation, no one gave you the answers. In fact, they didn't even necessarily give you the parameters because no one knew them.

You were told to produce a solid, unique contribution to science and knowledge, and then put on the spot to defend it. So said slightly less scientifically, you got this. We're all in unchartered waters here.

I feel confident that continued collaboration between industry and FDA will

result in sensible, justifiable and scientifically-robust research.

My conclusion, and I would give the advice to all of you who are preparing PMTAs or research in support of any of the two market pathways, number one, do not think you know what FDA needs. Do not assume you are the experts. Do not try to figure out what part of FDA's suggested rule and guidance matter.

Instead, do your best to be comprehensive. Be a positive collaborator. If your product is truly appropriate for public health, you should not be hesitant to provide as much information as possible.

Don't give FDA a reason to reject your product by omitting information deemed important. Give them reasons to engage in dialogue with you in the event that your data and conclusions do not result in a slam-dunk, no -brainer approval. Thank you.

DR. CECIL: Thank you, Steve.

MS. TALBERT: Good morning. My name

is Emily Talbert. I am a Lead Health Communications Specialist in the FDA Center for Tobacco Product's Office of Health Communication and Education.

I advise on a range of regulatory policy projects that include evaluating tobacco product advertising, marketing and promotion. And I help determine what are the appropriate marketing restrictions on a product-by-product basis such as those that might be put into a marketing-granted order for product receiving approval under PMTA or a modified-risk tobacco product application.

DR. MURPHY: Good morning. My name is Iilun Murphy. I'm the Director for the Division of Individual Health Science. The staff involved in Division of Individual Health Science include medical officers as well as behavioral and clinical pharmacologists. I'm in the Office of Science at CTP.

DR. ROSENFELDT: I'm Hans Rosenfeldt. I'm the Deputy Director of the Division of Non-

clinical Science and we have toxicologists and environmental scientists.

DR. CECIL: Thank you very much. All right, we have a series of different questions. We'll start with a simple one, if there's such a thing. So, it's a long question however.

So for literature reviews, you mentioned a bibliography should be included. Should full texts of the published works be included, and if so, how do you deal with copyright?

DR. ROSENFELDT: So, I do not know about the copyright, but I do know that it would be helpful to have the full text if possible.

DR. MURPHY: Generally speaking, if you go to any library, the library pays for access to journal articles. So you should be able to download the full text and be able to provide that to the FDA. I'm not sure beyond that what other information there might be.

DR. CECIL: For the industry colleagues, does that present a problem? I just

wanted to double-check.

DR. ROUND: Well, I will say that, I mean, the literature references can be numerous, and so --

DR. CECIL: And voluminous, yes.

DR. ROUND: -- if that is what the Agency prefers, we would certainly do that. But just note that it will be a lot of information.

DR. CECIL: That is fair. Okay, we'll move on to the next question. Yet another, I think, relatively straightforward. The IQOS PMTA included data unavailable for U.S. ENDS. What is the minimum available information required for an ENDS PMTA?

(Off-microphone comments.)

DR. CECIL: Oh no problem. I can repeat it if you'd like. Certainly.

The IQOS PMTA included data unavailable for U.S. ENDS. What is the minimum viable information required for ENDS PMTA? It depends on what the topic is I supposed.

DR. MURPHY: Right, I don't think

there's an answer to that. There is no required minimal viable data that is prescribed. So again, as a panelist noted earlier, please provide us, you know, supportive information that would render your product appropriate for the protection of public health.

And how you put that package together is going to be variable. It really is dependent on the product type and the design of the product. I mean, there's so many parameters that are important in the consideration of what the kinds of information that would be relevant for your application.

DR. CECIL: Okay, now we'll get in. Inclusion of labeling changes in post-market reports suggest that a label can be changed without a supplemental PMTA, is that so?

DR. MURPHY: So, a labeling change does not make a new product necessarily. So that label changes can be made and can be provided in part of the post-market reporting. But it is important to note that the label change cannot

violate, right, regulations that are in place, for example, modified risk.

So you can't have new modified risk statements that haven't been authorized in your labeling. So if it's maybe graphic changes or font changes, things like that, that's something that could be part of your post-market periodic reporting.

DR. CECIL: Okay. So I'm afraid this one is coming back to me already. What are acceptable sample sizes in a PMTA study? -- I can have a go at it if you don't want to. Go ahead, Hans.

DR. ROSENFELDT: Actually, I think it would be best if you had a go at it since this a product science-type question.

DR. CECIL: It is. So the size of the -- a sample size will depend upon the product. Clearly, an e-liquid will have a different need than an ENDS device will need because we're looking at a number of different factors in an e-liquid that are different than from a device.

Obviously, the HPHC yields are something that we do want to be looking at. We are using this to verify the results that we've received. We are not going to be asking in all likelihood for all of the products that are in the submission because we are looking at a sample.

I believe that from at least the two submissions that have been -- well at least two of the folks on the panel have been part of those -- the sample sizes are not tremendously large.

Our goal is not to have a huge cost burden to these things, but I can't say exactly how much it will be. Obviously, there's chemistry testing on the other end, and we do want to try and keep it to an approachable number. Jason, do you have a perspective?

DR. FLORA: I think it would depend on the product. If you're talking about product testing, you would have to take into account the variability of the product. If the product is very consistent, you would need less replicates

in your measurements, where a more variable product would need more replicates to provide representative data.

DR. CECIL: Right.

DR. MURPHY: Todd, I wanted to clarify. Is that question related to just sample testing or sample size in relation to studies, because those are two different types of samples we're talking about in sample size.

DR. CECIL: It is not clear, so you may take either side. In fact, why don't you go ahead and answer that question too.

DR. MURPHY: I'm volunteering myself, I suppose. So in terms of clinical study sample size, if that question is relating to that, I would say it depends on the study and the study design, and what your objectives are, right. So if it's a -- for example, a clinical study looking at use behavior, that would require maybe one certain sample size.

Looking at appeal and perception, another abuse liability study versus kind of

population level study. I mean it really depends on what the nature of the study is and what you're trying to get out of it.

So it's really important to be clear on your study objective and the statistical analysis plan to support that and justify your sample size that you provide.

MR. SEIFERHELD: I'll add to that as well. But following up on your comment, you know, statistical science provides ample methodology to determine sample sizes based on objectives and what sort of either metrics you're trying to calculate or differences in metrics you're trying to compare.

I would strongly encourage people who aren't familiar with that science to either engage a consultant or to refer again to literature. There are numerous examples of research out there that provide sample sizes and rationale for using them.

So rely on what's out there, rely on statistical science, because no one will ever be

able to give you an exact number as an answer to that question.

DR. ROSENFELDT: And I would generalize this even further and just state that it's important to spell out your methods clearly so that they can be evaluated so that one can interpret the study results.

DR. CECIL: Great. Okay. I'll take an online question. I'd like to thank Christina Saba for summarizing the approved PMTA for PMI's IQOS. Would CTP consider publishing reviews of approved PMTAs similar to CDER's publishing approved NDA reviews? Doing so would allow sponsors to learn from experience of successful applicants.

DR. MURPHY: I would note that the technical project lead reviews are posted. They're redacted for commercial confidential information, but they are posted so you can get a general understanding of the scientific data that was provided and analyzed to reach the conclusion and the determination of the Agency.

So I would encourage you to use that as a basis for understanding kind of the thinking behind the scientific decision-making process.

DR. FLORA: I'll add to that. I think the TPLs, reading the TPLs that are available is extremely helpful in understanding the Agency's current thinking on the variety of studies that are included in the PMTA. I think they've been really helpful.

DR. CECIL: All right. Thank you very much. That was useful. Once one ENDS product is approved, will FDA consider that ENDS product the most important comparative product?

DR. ROSENFELDT: So as I mentioned in my talk, the comparator product really -- you'd have to -- it would be helpful to understand what the users of the new product would be -- what would use. If that makes sense.

DR. MURPHY: So I would add to that and say, for example if, just hypothetically, if the first authorized ENDS product is a tank system, right, and yours is a closed system,

would the open tank system be the most appropriate important comparator? I would say not necessarily, right?

So it really depends on your proposed product and what the most likely user, you know, would be using if that product was not available. So think about it maybe perhaps that way.

DR. CECIL: All right. Please outline the clinical studies CDP expects to see in a PMTA, and I think Hans hit that to a certain degree earlier. It seems yesterday that it was stated that no clinical studies are required.

DR. MURPHY: So there are no required clinical studies, you know. The statute does not prescribe any sort of clinical studies that must be submitted in order for the Agency to make a determination. However, there are many studies that would be helpful for us to better understand your product.

So again, depending on what your product is and what kind of available information there is, if there are any gaps then it would be

very helpful for you to fill those gaps with any sort of studies that might be appropriate.

The ENDS final guidance that's available really tries to outline the spectrum of studies whether it's non-clinical studies or clinical studies to kind of help fill that story.

But depending in what information you have, then it's up to you to determine, you know, what studies might be helpful to conduct to again make a full picture to support your PMTA.

DR. ROUND: I'll just note that there seems to be a bit of a discrepancy between the final guidance and the proposed rule in that account, because it does look like there are at least two clinical studies that are proposed to be required by the proposed rule which would include a human abuse liability study and an actual use study.

So, I know that this is still out for comment and you're potentially still considering that, but I'm just wondering if you would comment on the discrepancy between the two?

DR. MURPHY: Sure. So the, as you know, the final guidance is just recommendations of things to consider specific for ENDS products, and the proposed rule, I think, is a little bit more comprehensive in terms of our experience and the kinds of studies we believe would be helpful to support a PMTA.

That being said, we are considering all public comments. And if you have concerns or comments, please send them in. And we take each comment and consider it, and then apply it to, you know, how we're shaping the proposed rule in terms of getting it to final rule.

DR. CECIL: All right. Okay. This is a long question, so bear with me.

As evidenced by FDA's Real Cost Campaign, the Agency appears to believe that teens who vape are more likely to start smoking cigarettes. That was in quotes. Should we read this to mean that the company submitting PMTAs for ENDS products will need to dispel this general understanding in addition to showing

product evidence that over their lifetime, youth aren't taking up or switching?

DR. MURPHY: I think people are looking at me to answer the question. So what I would say is that we know that youth use of electronic nicotine device systems is very problematic and concerning, right.

So that the, I think what's important is that applicants address how they are going to restrict youth access and youth use. Whether, you know, are there marketing -- what are their marketing plans. What are the age verification plans.

I mean these are some of the kinds of things that you might want to take time to describe in your application to ensure to FDA that your product will not kind of exacerbate the current situation in methods to curb and improve limiting youth access.

MS. TALBERT: I would just add that tobacco product advertising can blend across categories. So in the advertising that you're

developing for a specific product, it may be worth considering how it may influence youth tobacco use more generally as well. And as already stated, focusing on how you will limit youth exposure to the advertising is critical.

DR. CECIL: All right. We're going to leap to a new topic now.

What human factors foreseeable misuse assessments apply to bottled e-liquids? If we have the answer to that.

DR. ROSENFELDT: I can give it a shot. I think the first and most important thing to point out is at the moment, there is no information, no recommendations available.

I would suggest that there are -- you can tackle it from the point of view of the risk to the user and the nonuser and their container closure systems, child safety protection. Things like that could be useful in an application.

DR. MURPHY: So I think this would be a good example of a case where bridging would be, you know, a viable method, right, instead of

doing human factor studies on your product. I mean there are many situations.

We have containers that contain toxic substances. So you can bridge to existing studies that show ways that manufacturers have limited accidental exposures, right.

I mean understandably for a bottle containing high concentrations of nicotine e-liquid that accidental exposure would be one of the largest concerns. But that, again, there are other studies you can borrow from and adapt to your situation and kind of describe how the steps the manufacturer is taking to, again, limit the accidental exposure.

DR. CECIL: Okay. I'm going to change one of the questions we received a little bit here.

So the question is, will the FDA allow manufacturers to bridge data from a six milligram to a zero milligram, assuming that the results are tested two, four milligrams also available from the same flavor.

The question I want to modify slightly is how would the industry panelists suggest that we look at bridging data? What kind of bridging data do you think would be appropriate for submission?

Obviously, you've made submissions or you will have made submissions. And so I'm curious how do you think we should address bridging?

DR. ROUND: Can I ask a follow-up question to that?

DR. CECIL: Certainly.

DR. ROUND: Which is, you said a six milligram versus a --

DR. CECIL: Zero.

DR. ROUND: -- zero milligram, is this -- is there any detail --

DR. CECIL: With two and four in between. I think the idea was there's zero, two, four, six milligram nicotine presumably.

DR. ROUND: Should we make some assumptions around closed versus open container?

DR. CECIL: You may.

DR. ROUND: Okay. Pretty general. Well I would say first of all, that is one area I think in the final guidance there is some discussion around, you know, bracketing high and low nicotine concentration products, except for the rest of the product is exactly the same.

There is the suggestion anyway that we could do that. That an applicant could test the high and low and then bridge the in-between.

(Off microphone comment.)

DR. ROUND: Oh sure, thank you. That the applicant could test the high and low, and then bridge the in-between. And I think that seems like to be a good strategy, especially if FDA is behind that.

DR. CECIL: Is FDA behind that?

DR. ROSENFELDT: I think that would probably work out for the FDA from a toxicology point of view. I don't know whether Iilun has anything more.

DR. MURPHY: So again, it really

depends on the type of bridging I think from the toxicity perspective. You know, they're usually concerned about the highest level of risk, and so the highest level of nicotine may be appropriate.

From our perspective, from the Division of Individual Health Science, we're looking at exposures in terms of use behavior and so, you know, we are often interested in typical use, right. So what is the most likely typical use that a user might have.

And so only testing the highest level may not, you know, represent kind of typical use behavior. If you're able to do the low and high end, bridge it to, you know, what's in between, you can justify it that should be sufficient.

But I might even go to suggest that, you know, medium-low, medium, and high levels of nicotine. Because I think that you could have, it really depends on the variety you expect to market, right.

So if you take, you know, if you have from zero to 34 mg per ml, and you have every

possible level in between, then I think that kind of, a little bit more, not just low and high, but low, medium, high exposures in testing may make more sense.

If you have very limited, you know, range then, maybe low and high may be appropriate. So I think that it depends on the range you're trying to evaluate and the number and types of products may be part of the consideration.

DR. ROSENFELDT: I would also add that dose response matters, and you know, it depends on where you are on the dose response curve. Nicotine is just one of the toxicants that we would be concerned about.

And so, if there were, for example, differences in the flavors and other things that are in say an e-liquid, that would be something that we would consider.

DR. ROUND: So then it sounds like bridging is getting pretty difficult in that scenario then, especially if you have different

flavor. I mean, I know we talked about the scenario of bridging nicotine strengths, but then there's also the issue of flavors that you just mentioned.

So, I guess with the additional complexity, the more difficult it gets to actually be able to effectively employ bridging.

DR. ROSENFELDT: And that's where we would ask, or I would suggest that a rationale might be helpful for why you think that, you know, using a product that is not the product under review to test, applies to the evaluation of the new product.

MR. SEIFERHELD: What about the utilization of what I'll call statistical experimental design methodology? If you have a number of factors here that we're talking about, you know, arguably you could be doing some testing at low and high levels of certain parameters, maybe a midpoint for example, and use just fundamental statistical modeling on the output. Is that something that FDA considers a

reasonable approach in the context?

DR. ROSENFELDT: So, the way I would think about it is this way. I would say that it's one thing to talk about sample numbers and to talk about, you know, the 95 percentile confidence interval, for example.

It's another thing to talk about the hazard posed by a particular flavor or chemical, you know, that's in one product but not in another product. That's a different kind of analysis.

DR. ROUND: It also sounds like, from a bridging perspective anyway, that there is a difference between when you're considering the toxicity of a product versus the individual health impact of a product.

DR. MURPHY: Right. So there is different bridging, right. And depending on the kind of information you're trying to bridge from, I think it depends the level of information that you would need.

So, for example, if you're going to

do, if you're going to describe your product into analytical testing, there's going to be kind of one level of bridging information.

And then depending on clinical study information, if you're trying to bridge to a clinical study, depending on the kind of study it is, maybe just general bridging information is sufficient just describing it's a similar closed-system ENDS product with PG, VG base and a flavorant, you know.

Whereas, if you're doing analytical comparison of one product to kind of a representative market comparator, then you might need a little bit more specific information. For example, comparing HPHCs between your product and comparative marketed products, you know, that's a different level of bridging.

DR. ROUND: Since you mentioned comparator market products and the idea of bridging to those, and I included it in my remarks, but I'm just -- Dr. Rosenfeldt, I know you mentioned that for an effective bridging

argument, you'd want things like engineering specifications and ingredient listing.

So, if we don't have that for a product that there's published literature on, but we certainly know what are the omissions of that product, would it be appropriate to bridge?

DR. ROSENFELDT: So it really depends on the context as Dr. Murphy just mentioned. It depends on the study, the kind of study for example.

So for example, I would imagine, and Dr. Cecil can correct me, that if one product was being substituted for another product for the purposes of looking at HPHC yields, that it would be helpful to have very good comparisons between, very defined comparisons between one product and the other product, that they are the engineering specs, and other detailed chemical analyses would be helpful.

In other situations, it might be less -- you know, you may need less definition. For example, potentially, HPHC deliveries might be

sufficient in a scenario where you've got -- you're looking at one test article that is, you know, substituting for another test article in a toxicology study.

I would add that ingredient information would probably be helpful in that scenario as well, but the level might vary depending on the context. I hope that makes sense.

DR. MURPHY: You had asked a question, I think, you know is bridging really limited to, you know, within manufacturer because of the level of information that would be needed? And I would say no, that bridging is, again, variable in terms of the level of information that's appropriate.

For example, in the case of like a smokeless tobacco product. You know, if a manufacturer is comparing to let's say the top 10, you know, market sellers, I think there is sufficient publicly available literature to generally say what the HPHC levels are generally

are in these products, or cigarettes for that matter. We kind of know what the general range of different HPHCs are for cigarettes.

Likely, with ENDS products, they think with time will have even more information, but already there is some available information about kind of popular ENDS products and what their HPHC levels are because there's articles comparing ENDS products to cigarettes for example, right.

So, you know, if you are bridging a prototype of a product to the latest, you know, model that you're proposing, then we expect you to have much more detailed bridging information, right, because you have that. That's at your disposal.

I think we understand that, you know, we stay on top of the literature. We understand what's publicly available generally, and what would be reasonable to have available as comparator information.

So, I think that generally you do what you can with the information that you have. You

provide rationale for why you're using the information that you're using. And then also talk about limitations of your approach. And we'll assess the totality of the information to see if your conclusions are appropriate.

DR. CECIL: At the risk of belaboring the question on bridging, the question for clarification that came up. And it seems that bridging and bracketing are being interchanged in this discussion.

These constitute different assumptions and considerations, correct? And I think, again, from a chemistry perspective, when we talk about bracketing, you are bridging. You're making a statement that you're testing low and high, and that there is a linear relationship between low and high. That's a bridge.

So even though I think bridging considerations for clinical and non-clinical are different than bracketing situations for chemical and engineering aspects, they are one and the same, just the flipside of that same coin.

So I did want to bring that question up, and then shift to another topic. I actually love this. This is a great discussion and we can come back to it again as we continue to hear more discussions and questions that come through, but I want to make sure that there are other questions here that are handled as well.

So, for ENDS hardware manufacturers, how extensive HPHC and toxicity testing should be considered since they don't manufacture e-liquids?

DR. ROSENFELDT: So again, currently we have no regulations that are final. I would suggest that at this time it would be useful to have HPHC, aerosol-using e-liquids that are, you know, would be used in the context of the product that is under review.

DR. MURPHY: Yes, the ENDS final guidance does go into e-liquid versus device considerations, and so we definitely would refer you to that. And also the proposed rule has some thinking behind our current, you know,

recommendations.

I think the one other thing is that, you know, again, if you're a device manufacturer, pick a representative e-liquid that you think might serve as a good product. And then what we're interested in also is like extractables and leachables, right. So are there any sort of metals that, you know, get aerosolized in the product when it's heated compared to, you know, so if you have an e-liquid, what we want to know is when, you know, somebody uses your product what happens to it when it gets aerosolized and is there something unique about your product. So, I think that sort of information is important for us.

DR. CECIL: And we also know that many HPHCs are developed at the point where the coil and the e-liquid meet. And those HPHCs are what we're concerned with in every ENDS product. Every ENDS device is different.

And the effects of the ENDS device, the coil, the batteries, the rate at which it

heats, the coil temperature, all affect the HPHC yields which therefore affect the user.

And so I think there is a lot of interest in ensuring that we understand what likely HPHCs will come from devices.

MR. SEIFERHELD: If you flip that question kind of on its head, and you take the position of the e-liquid manufacturer, what is the expectation, you know, in the other direction. There's obviously other multiple devices you could test through.

So if, you know, is there an expectation and the e-liquid manufacturers are picking one, you know, typical device. And if so, is there an expectation of aerosol testing and what comes out of that device based on the e-liquid, or does that fall back to the device manufacturer?

DR. MURPHY: Again, we have put these considerations out on the ENDS final guidance, and so to refer you back to the final guidance for details on that.

But I think that, again, for e-liquid manufacturers from the FDA side, it would be informative for us, for us to understand as the e-liquid manufacturer, who is your intended consumer, right? If your intended consumer is for a certain device or product user, then we would like to know, well when it's used with that device, what is the actual exposure to the consumer?

DR. CECIL: For open-system devices, how many e-liquids should each device pair with to do the testing? What does a reasonable range mean from within the FDA guidance?

DR. ROSENFELDT: Todd, can I punt this one to you?

DR. CECIL: You can. Well, I'm going to actually steal a quote from Dr. Benson. It's one of my favorite ones, which is, PMTA is your chance to tell us your story. You identify what is the most appropriate e-liquid or e-liquids to use. You tell us why those are the most appropriate e-liquids that you chose.

Our understanding of why you chose the route you chose helps us understand your product better. Helps us raise questions about what it is doing. And the data you provide hopefully provides all the answers we need.

So I think that is a tremendous quote from Dr. Benson. I want to say thank you. I've used it over and over again.

DR. ROUND: Can I just add --

DR. CECIL: Please do.

DR. ROUND: -- perhaps, or maybe ask. I assume that's the case for any PMTA for example, not just one, you know it's open-liquid specific or something like that. I mean it is our responsibility as the applicant to tell FDA why we believe -- why we've chosen the data or the studies that we've chosen and why we believe our products are appropriate for the protection of public health.

DR. CECIL: You're absolutely right. They can't hear me nodding. Anyone want to add on more to that? All right. Let's move on to

labeling. There's a couple of questions here on -- there's actually many questions here on labeling, but I'll ask a couple that are here.

Does non-prescription drug products 2010, guidance I presume, apply to ENDS and e-liquid labeling comprehension studies?

DR. MURPHY: I can't remember if it's the 2010 OTC guidance, but definitely there are a number of labeling comprehension study guidances that are available by other FDA centers that are applicable.

You just have to take, you know, what's relevant and apply it to our situation. It's not going to be 100 percent applicable because, again, for OTC situation you're really looking at, you know, patient selection, right. And there's other factors that in terms of, you know, are the right people, you know, diagnosing themselves correctly and can they follow the instructions, et cetera.

So, in the situation for the tobacco products, it's not really exactly the same

situation as in over-the-counter non-prescription medication selection in following label situation.

But I think there are a lot of concepts in terms of how to conduct a label comprehension study that can be applicable, so take what's appropriate.

Similarly for human factor study, CDRH, so Center for Devices and Radiological Health has guidances on how to conduct human factor studies. And I think a lot of concepts can be borrowed and applied for tobacco product studies.

DR. CECIL: Okay. So many good questions. This one is a clarifying question, so I thought we'd go ahead and add this one.

Dr. Rosenfeldt made an argument of the ENDS industry to find new products not under review to be used as comparative products for bridging data and population studies. Is the FDA pushing PMTA applicants to not use the HPHC data already on record from combustible tobaccos?

ENDS was offered as a cessation to smoking combustible tobacco. Why would we not use the data on record that HPHCs are significantly lower with ENDS?

DR. ROSENFELDT: Okay, so I think that, again, the point is what would the best comparator be. If there are data indicating that folks would switch from tobacco, from cigarettes to an ENDS device for example, then those data that are published for cigarettes might be applicable.

If, you know, it would be helpful to have a rationale as to why the applicant thinks that published data applied to the comparison between an ENDS product and the published cigarette literature. I think that answers the question.

DR. CECIL: All right, great. We've got a couple of questions here that have to do with nicotine metabolites. I'll read you both of them because they both ask basically the same.

So, Dr. Rosenfeldt listed in his table

earlier in the presentation that nicotine and nicotine metabolites were measured. Routinely, PK studies measured nicotine throughout, and metabolites such as cotinine at baseline only. Could Hans elaborate on the expectations re: metabolites?

And the second question is, why would you want to measure a nicotine metabolite in a behavioral pharmacology abuse liability study? So I think they are associated.

DR. ROSENFELDT: So the second question about why metabolites would be measured in an abuse liability study, the details of that analysis are beyond my expertise. I'm not a behavioral pharmacologist.

But, I would say that it would be helpful in a PMTA to have the profile of user exposure to nicotine. That is something that we usually consider.

DR. MURPHY: I mean to the best that we can, we like to understand kind of full exposures in all the nicotine as well metabolite

exposure that may impact use behavior and health impact.

If you are only looking for certain exposures, then again say why and, you know, provide your justification why you are limiting. I mean, we understand that there are practical limitations in any study as to what you choose to prioritize in terms of measurements and endpoints. So again, it's a matter of justifying your decisions that you make.

DR. ROUND: I'll just add I had a similar question about the nicotine metabolites. I certainly understand the need for that in an abuse liability study understanding kind of what nicotine uptake looks like from a given product.

But I mean the pharmacology of nicotine and metabolism of nicotine itself has been known for many years. So, I'm thinking that we wouldn't as applicants need to reinvent that wheel in every application.

DR. ROSENFELDT: I would add though that the exposure profile can vary by product

depending on the route of administration and other factors.

DR. ROUND: Yes, I definitely agree with that, and specific to nicotine and seeing what nicotine -- what happens to nicotine in the body. At least nicotine levels itself. But I mean looking at, I mean there are a bunch of different metabolites that might not have relevance to abuse liability, for example. So focusing on that seems to be relevant.

But kind of looking at the numerous different metabolites at different points in time, for example, may not be relevant to the abuse liability of a product.

DR. CECIL: This one's a hard one. Okay. If a TPMF, so we're turning back the way back machine a little bit, is submitted by a flavor company including ingredient list, and the ENDS company submitting a PMTA does not know the proprietary ingredient list, how should the ENDS company demonstrate that it is safe from a toxicological evaluation or assessment

perspective?

DR. ROSENFELDT: So both the TPMF and the PMTA will be reviewed. If there is an issue with the TPMF, my understanding is that the company will be -- the PMTA submitter will be notified. I believe that is what will be happening.

DR. CECIL: That is correct. I'm not sure that it actually gets to the heart of the question, but I'm not sure there is a good answer to this question necessarily. Because when we talk about the toxicity of flavors, we are dealing with the fact that flavors, even though they're stated to be grass, are not designed to be inhaled.

And the toxicity levels of flavors may be unknown in the general literature. So in general, how would one go about doing a safety assessment or toxicological assessment of a flavor if, say, you're a flavor company. I can turn to you all as well. How do you approach this?

DR. FLORA: So it sounds like the question is you would have a list of ingredients, proprietary ingredients in the TPMF, that then the applicant would not be aware of and be able to conduct a toxicological evaluation of those ingredients.

DR. CECIL: Right. They're purchasing that flavor mix.

DR. FLORA: Right. I would recommend that the flavor manufacturer have a consultant conduct the toxicological evaluation. Certainly the applicant can do in vitro studies and HPHC evaluations of the aerosols. But ideally, there would be a toxicological evaluation within the TPMF.

DR. CECIL: Right.

DR. ROSENFELDT: I guess, I mean I think that at that point, it's really between the applicant and the manufacturer of the proprietary flavor compound.

DR. CECIL: So we are running out of time. I think we're going to end at 10:15, which

is a little ahead of time. That's still over an hour for this Q&A. I want to give our panelists a chance to relax.

But before we do that, let's hit them with at least another question or two. And I think this one for the industry panelists, and I'm going to paraphrase. It's a long question.

This individual asked, said we have 400,000 SKUs and all e-liquids. How would you recommend that they trim down the number of applications they need to submit, or the number of the amount of testing that would be necessary to a point at which it is achievable from their perspective? Or from your perspective?

MR. SEIFERHELD: They might want to start by looking at what they sell the most of because, I mean the idea of 400,000 is simply inconceivable. And sometimes it just has to be a harsh reality check of what sells the most, and then what kind of competitive angle they want to take in the marketplace.

You know, in terms of what are the

varieties that other companies are going to manufacture and what role do they want to play in the space. That should at least help wipe out a few digits on the number? I'll let you guys chime in if you want from there.

DR. FLORA: Yes, it's a tough question. It's a lot of products and I think I agree with Steve on prioritization would be the recommendation that I would make. You know, it's a high standard but it needs to be an achievable pathway, but I think the number that you gave is a pretty outrageous --

DR. CECIL: It's a big number.

DR. FLORA: So, yes, obviously prioritization would be the first approach.

DR. ROUND: I'll chime in that I agree with all of that. I think there's some other factors that you could consider. I mean obviously you've probably got a long list of ingredients to consider there if there's anything that might be of particular concern to FDA. I think that would be a good way to pare that list

down.

We talked about bridging a fair amount already this morning and bracketing. Those would be good ways to pare that down as well.

DR. CECIL: I concur. I think we also heard design experiments is another way to attack it, and I think that is a viable option. And you're right, bridging and bracketing are ways to get a smaller number.

Again, you'd need to show across a product line or one flavor profile. The e-liquid PG VG combinations for instance can fall out because they're going to be similar, which leaves you with the flavors you have to deal with. Which will bring down the amount of information tremendously.

So I think it is approachable. It is consumable if you like. But there are some tools you need to apply. I think you've all talked about them.

So with that, let me go ahead and draw this panel to a close. These other questions

that we received and any others that we receive, we'll go ahead answer those after the meeting's over.

And we will go ahead and take a 15-minute break. Be back here at 10:30 to begin session four.

(Whereupon, the above-entitled matter went off the record at 10:14 a.m. and resumed at 10:37 a.m.)

DR. CECIL: Good morning. Now that my mic's back on again, I can actually talk to you all. I think we're a little bit longer break than intended but that was on purpose. We give everyone a chance to get ready for a shift in our program.

So up until now, we've been talking largely about the PMTA process in the end of the session yesterday and today. We're now going to talk about the Substantial Equivalents pathway, and we'll have four presentations followed by a panel discussion after lunch. So let me go ahead and start this with Lauren DeBerry who will be

our first speaker.

MS. DeBERRY: Good morning everyone. Can you all hear me? Okay. If at any point you can't, shout it out because I tend to try to run away from the microphone.

My name is Lauren DeBerry and I'm a Regulatory Health Project Manager in the Office of Science. Today I'm going to talk to you about the Center for Tobacco Products Substantial Equivalent Program also known as the SE Program.

First, I will provide an overview of the SE Program, then we will discuss program updates, and finally we will share SE metrics. To begin, let's go over the Substantial Equivalents Program.

The statutory authority for the SE Program can be found in the Tobacco Control Act. It provides the framework and standards for the SE Program.

SE applications are a comparison between the new tobacco product and an eligible predicate product. For determination of

substantial equivalence, the manufacturer must demonstrate that the new product has the same characteristics as the predicate product or has different characteristics than the predicate, but the new product does not raise different questions of public health.

This means the new tobacco product must be equal to or better than the predicate product in terms of health effects for the population.

There are two types of SE reports, provisional and regular. Provisional SE reports are applications for new tobacco products that meet the following statutory criteria: SE reports were submitted by March 22, 2011 and the products were introduced or delivered for introduction into interstate commerce after February 15, 2007 and prior to March 22, 2011.

Regular SE reports are applications for new tobacco products that are not eligible for provisional status. At this time, all provisional SE reports are either under review or

closed.

It is important to note that SE reports for deemed products will all be considered regular reports as their applications were not eligible for acceptance at the March 22, 2011 deadline. These products include cigars, pipe tobacco, water pipe, ENDS, and other regulated tobacco products not included in the TPA.

The SE review process has three phases that can be broken out into multiple steps. Application review includes Phase 1, Acceptance; Phase 2, Notification; and Phase 3, Review and Action. Unlike the PMTA process, SE applications do not have a filing phase. Now we will go over each phase in greater detail.

Phase 1, Acceptance. In this phase, we will receive and review your SE report to determine if it's under CTP's jurisdiction and meets all statutory criteria.

The reviews to accept procedures for pre-market tobacco products submissions rule,

also known as the RTA rule, applies to all applications. FDA will refuse to accept an application if any of the criteria listed here are missing.

The RTA rule was discussed during the PMTA presentation given yesterday by Ms. Busta. For additional information about the rule, please refer to her presentation or the rule in the Federal Register.

For this presentation, we will focus on the additional requirements for SE reports. FDA may refuse to accept an SE report if the following additional criteria are not met.

Basis for SE. All SE reports must provide basis for Substantial Equivalents, either same characteristics or different characteristics.

Health Summary Health Statement. All SE reports must contain either a Health Summary or a Health Statement. This is not the same as submitting tobacco health documents under 904(a)(4). A statement that you do not have

documents regarding health or behavioral effects is not acceptable.

The application must include scientific literature or an actual summary addressing the health effects of the tobacco product or include the health information statement that states information will be made available upon request by any person.

Compliance with 907. For compliance with Section 907 of the FD&C Act, the application must provide information regarding how the product complies with all applicable product standards.

For example, addressing characterizing flavor and federal pesticide chemical residue standards. For characterizing flavor, all applications must identify the product's characterizing flavor based on the RTA rule.

This flavor may be of a variety of allowable flavors for your product category including tobacco or none. However, certain product categories such as cigarettes and roll-

your-own must also comply with product flavor standards.

For pesticide chemical residues, currently there are no federal laws specifying pesticide chemical residue standards. Therefore, this additional rule does not apply at this time.

Environment Assessment. The Office of Science requires all SE applications to provide either an environmental assessment of their tobacco product or a valid claim of categorical exclusion. All regular reports require an environmental assessment. Claims for categorical exclusion are only available and valid for provisional SE reports.

Your environmental assessment must contain the following elements for acceptance for the SE Program: the environmental impact of the proposed action, impacts related to use, and impacts related to disposal of the product. For more information about the environmental assessment needs, please see Dr. Rosenfeldt's presentation earlier this morning.

Next we will discuss Phase 2, Notifications. Again, please note that SE reports do not have a filing phase. During the Notification Phase, FDA conducts a review to ensure that the predicate product is eligible.

A predicate product should be either a tobacco product that was commercially marketed other than for test marketing in the United States as of February 15, 2007, also known as a grandfather product. Or a product previously found substantially equivalent by the FDA.

Generally, once accepted, your application is under review. To change a predicate product after acceptance, a new application is needed.

At this time, notification phase, Phase 2, and review phase, Phase 3, run concurrently. If we were to receive large volumes of applications in a short period of time, we may pause review after acceptance in order to determine review order for scientific evaluation.

Now I will briefly discuss provisional products. Those of you who have submitted applications for provisional products may note a slight change to the notification phase. All provisional applications are now in substantive review or closed.

In response to then Commissioner Gottlieb's comprehensive plan for tobacco regulation, the Office of Science assessed a host of factors to determine which new tobacco products subject to provisional SE reports have the greatest potential to raise different questions of public health.

Some considerations included, for example, whether the new product had a significant increase in any harmful and potentially harmful constituents compared to the predicate product.

As a result of this evaluation, we continue to review those provisional products that we've determined have the greatest potential to raise different questions of public health,

and have removed from review over 1,000 provisional SE reports.

These applications, the ones that were removed from review, are considered closed unless the applicant takes action that would require review. A full list of products that have been removed from review is available at our website.

Now we will move to Phase 3, Review. The purpose of the review phase is to conduct scientific assessment to determine if the new product is substantially equivalent with respect to the predicate product.

Generally, SE reports are assigned chemistry, toxicology, engineering and environmental reviewers. Additional scientific evaluation may be needed as decided by the technical project lead. For example, additional reviewers can include social science, addiction or microbiology.

Upon completion of review, we will decide if the application contains enough information to make a final determination. If

enough information is not provided, we will issue a deficiency letter.

If enough information is provided, we will determine whether the new product is substantially equivalent, SE; not substantially equivalent, NSE, with respect to the predicate product.

After completion of review, the application will enter the action part of Phase 3. If the application is found SE scientifically, we will then address environmental considerations.

To grant marketing orders, FDA must prepare an environmental impact statement or a finding of no significant impact. If the application does not contain sufficient information, we will issue an environmental information request letter.

Once the environmental considerations are satisfied, FDA will issue the SE order letter and contact the applicant to offer a courtesy copy of the final TPL review, and the order

letter will be posted to FDA's website.

If the application is found NSE, FDA will skip steps 8 and 9, issue the NSE order, and contact the applicant to offer a courtesy copy of the order via email.

For applications that have been marketed prior to the NSE decision, the final TPL review and the order letter will be posted to the FDA website. For those products, FDA offers courtesy copies of the NSE letter, the TPL review, and the last cycle scientific review that supports the NSE.

FDA will delay posting the NSE order letter and the TPL review for 30 days to allow the applicant to review the courtesy copy.

For statutorily regulated products such as cigarettes or smokeless, there are two timelines for the SE process. For regular reports, the SE process should take 90 days. For provisional reports, the SE review process should take 120 days.

Phase 1 starts upon receipt of the

application and can take up to 21 days. Phases 2 and 3 start after acceptance concurrently, and can start prior to day 21. By day 90 or 120, FDA will issue either a deficiency letter, an environmental information request letter or an order letter.

Upon receipt of your amendment to the deficiency letter or the environmental information request letter, a new round of review will start and the timeline starts over at day zero.

Please note, FDA does not have time requirements for deemed products. However, we will do our best to maintain these timelines where practically possible.

Next, I will provide some program updates. On September 16, 2019, the Office of Science began issuing correspondence with new names and new formats. Please raise your hand if you've received one of these letters. Wow. Okay, that's a little better than I was expecting. Thank you. If you haven't received

one of these letters, you will.

The goal for these updates were to reduce confusion by using plain language to increase clarity by ensuring the purpose of the letter, and the next steps were up front to simplify and standardize language and letter format across all programs and to move supplemental information into the appendices.

To clearly identify the subject of the letter, FDA has updated our letter titles to better reflect application status. As shown in Phase 1, the acknowledgment letter is now the acceptance letter. This better describes the status of your application.

At the 2018 public meeting, FDA announced that the advice information request letter and the preliminary finding letter were replaced with a deficiency letter. This was done because with the new application response deadline, there was no longer a time difference between the two letters.

Our goal for these updates was to

clearly identify requested versus required information. Previously, we issued advice information request letters for environmental requests that precluded FDA from issuing marketing orders. Now we have a letter specifically for that circumstance.

The environmental information request letter is issued when the application has enough information to be found scientifically SE, but additional information is needed to satisfy NEPA. If we identify environmental requests earlier in review, we may include them in the deficiency letter.

Now let's look at an example of the deficiency letter. Change can be hard, but don't worry, some things will remain the same.

As always, the letter title can be found at the top right corner of the first page, and FDA will identify the tobacco products subject to the letter in the first paragraph. The second paragraph will identify the due date in bold typeface.

For SE reports, the final day to respond to the deficiency letter is day 180 after the issuance of the letter. In the third paragraph, FDA will notify applicant if the deficiency letter is their final deficiency letter.

If FDA states that it is not the final deficiency letter but your response provides enough information for FDA to make a final determination, we will not issue another deficiency letter. And note, deficiencies now begin on the first page.

You will also notice a change to the initiation of the next round of scientific review. FDA will begin scientific review 181 days from the issuance of the deficiency letter unless the applicant requests otherwise.

This means the applicant can submit a complete response prior to day 180, but FDA will not start review until day 181. If you would like FDA to begin review prior to day 181, in your response clearly state that you have

responded to all deficiencies and requests and you would like scientific review to start when FDA receives your response.

At the end of the letter, you will find your Regulatory Health Project Manager's contact information and a list of all appendices included in the letter. Appendix A will list all tobacco products subject to the letter.

Appendix B shows all amendments for the tobacco products subject to the letter. It also includes the status of those amendments.

Appendix C provides information to help applicants understand the requirements for providing health information. And appendix D provides instructions on how to respond to the deficiency letter.

Applicants should review all information in the letter to ensure that the information is correct. If there is an issue with the information included in your letter, please let us know. You can let us know by submitting an amendment or contacting your

Regulatory Health Project Manager. I hope this walkthrough will help you navigate the changes to the deficiency letter.

Next, I will discuss FDA's attempt to reduce the issuance of deficiency letters. On July 2, 2019, FDA released Scientific Review Policy Memos that provided details on key areas of regulatory science.

These memos provide valuable information to manufacturers on the different scientific disciplines and areas involved in application review. We hope this information will help you prepare stronger applications.

For more information about the scientific review policy memos, please refer to the presentation on the changes to the FDA website given yesterday by Ms. Redus, and you can also see these on our website.

In addition to the release of the review policy memos, FDA issued a proposed rule titled Content and Format of Substantial Equivalent Reports, Food and Drug

Administration's Actions on Substantial Equivalent Reports.

The SE rule would establish requirements for content and format of SE reports. This proposed rule also provides information as to how the Agency intends to evaluate SE applications. The comment period is currently closed. We are reviewing your comments and appreciate your feedback.

Next, we will discuss SE metrics and program accomplishments. I will not be discussing the performance goals for Fiscal Year 2019 or FY19 as we have open cohorts. We intend to post all performance goals in January 2020 similar to past years. However, I do have other metrics which may interest you.

The metrics are broken out into statutorily regulated products and deemed products for both FY19 and cumulative totals. Statutorily regulated products include cigarettes, roll-your-own, cigarette tobacco and smokeless. For reporting purposes, cigarette

tobacco is included in roll-your-own metrics.

As a reminder, FY19 runs from October 1, 2018 through September 30, 2019. As of September 30, we have received 229 applications, 62 of which are open which means they are within FDA's review process, and 167 of which are closed.

In the table on the slide you will see some of the most common types of closed action. Closed means there's nothing pending with the Agency. Other types of closure are listed in the footnote below.

This table provides cumulative metrics related to the SE program for statutorily regulated products. For clarity, cumulative reflects all SE applications received from the start of the center through September 30, 2019. CTP has received 6,324 SE applications for statutorily regulated products. Of those, 5,642 have been closed.

As previously discussed in the notification phase, FDA removed from review over

1,000 provisional products that were considered less likely to raise different questions of public health. These applications are considered closed and will only reopen if the applicant initiates review.

This table provides metrics for deemed products for fiscal year 2019. Deemed products include cigars, pipe tobacco, water pipe, ENDS and other regulated tobacco products not included in the TCA. We have received 73 applications, 51 of which are open and 22 of which are closed.

And finally, this table captures cumulative metrics for SE applications for deemed products. We have received 364 SE applications, many of which were received prior to FY19. Of those, 313 are closed.

A number of these were closed due to a lack of environmental assessment. Therefore, it is important that you include all required elements in your application.

As a reminder, deemed products are not eligible for provisional status, and therefore an

environmental assessment is required. As discussed earlier in my presentation, a valid claim of categorical exclusion only applies to provisional reports.

This concludes my presentation. Please find additional resources on the slide. Thank you for your time. I hope this presentation was helpful in the preparation of your future submissions.

If you have further questions, please hold them for the panel discussion or send them to your Regulatory Health Project Manager.

(Applause.)

DR. CECIL: Thank you, Lauren. Our next speaker is Bryan Hills, who'll speak to us about grandfather tobacco product reviews.

MR. HILLS: Good morning. All right. So my name is Bryan Hills. I'm Deputy Division Director for the Division of Promotion, Advertising, and Labeling. The division's in CTP's Office of Compliance and Enforcement at CTP.

Which button do I press? To the right? Perfect. Thank you. All right.

I'd also like to mention at the outset of this presentation, that we have many resources about grandfather tobacco product determinations on our website, including a guidance document and webinar. And I invite you to look at those for reference outside this public meeting or any time you're doing anything related to grandfather tobacco products. Whether that's part of a stand-alone or an SC report.

Also a reminder, this presentation is not a formal dissemination of information by FDA. It does not represent the Agency's position or policy.

So my presentation will be covering two types of grandfather reviews or GF reviews for short. And I'm sorry if I keep like looking around. I'm not use to this. This is very nice right here.

So first we're going to go into a GF review that occurs as part of the voluntary

stand-alone GF determination request program. Secondly, a GF review may occur under a substantial equivalence report or SE report for short, when a GF tobacco product is used as a predicate.

So very briefly, voluntary stand-alone grandfather tobacco product review occurs when a manufacturer submits a request to FDA to determine the grandfather status of their tobacco product or GF reviews may occur under an SE report when a grandfather tobacco product is used as a predicate product in determining substantial equivalence of a new tobacco product.

We'll mainly be discussing the process for reviewing voluntary stand-alone, grandfather termination requests since the review conducted for grandfather tobacco products and SE submissions is very similar.

Additionally, submitting as a stand-alone is beneficial because one, a GF determination may be made prior to submitting an SE report which can greatly facilitate the

predicate review for the SE submission. And two, it'll clarify the status of the tobacco product for manufacturing inspections.

So let's first talk about what is a grandfather tobacco product? Well, a grandfather tobacco product is a tobacco product that was commercially marketed, other than exclusively in test markets, in the United States as of February 15th, 2007. Just a reminder if -- and if you don't already know, FDA interprets the phrase as of February 15th, 2007 as on February 15th, 2007. And that's in guidance available on FDA's website.

So if your tobacco product was commercially marketed in the United States as of February 15, 2007, not exclusively in test markets, and you haven't made any changes to the product after the grandfather date, the product's considered a grandfather tobacco product.

GF products are regulated under the Federal Food, Drug and Cosmetic Act, but they don't require prior authorization to be legally

marketed in the United States. That's because GF products are not considered new tobacco products.

For new tobacco products, you would need to submit an SE application, an exemption to an SE or premarket tobacco product application to market your product in the United States. All right.

So let's now talk about our reviews of voluntary stand-alone GF determination requests. So an initial question may be who submits a GF determination request? Well, if you are a manufacturer and believe that your tobacco product should be considered a grandfather tobacco product and you'd like FDA to make a GF determination for your product, you may submit that request to FDA.

Now if you decide to submit this request, please account for the following before you submit. Grandfather status determinations are made for finished regulated tobacco products. By this we mean a tobacco product that is sealed in final packaging intended for consumer use. So

for example, a cigarette pack, a smokeless can, a five pack of cigars wrapped in final packaging for sale to consumers.

So FDA intends not to review GF submissions for regulated tobacco products that are sold or distributed solely for further manufacturing into a finished tobacco product. So that could be a cigar wrap to be used to manufacture a final cigar product.

As I mentioned before, a GF determination can be beneficial to facilitate SE reviews and help you during manufacturing inspections. And I also want to stress that submitting a request for GF determination status is a completely voluntary program under the voluntary stand-alone GF request.

Okay. So if you believe your product is a GF and you would like to submit a request for GF status determination, here are a few things you should remember. We recommend that you include the following in your request. Submissions should be labeled as grandfathered

submission and you should identify the applicant's name and the name of the product as it was commercially marketed in the United States as of February 15th, 2007 to help easily identify your request.

If you're submitting more than one request, submit each tobacco product as a separate submission. And please submit your request electronically through CTP Portal or mail it to CTP, DCC. Additionally, please utilize the resources that we have on our website. Our guidance document regarding GF products. And also the stand-alone GF webinar that we have online.

And if you have any questions about the voluntary GF you have submitted, you can send any questions you have to the email address above, ctp-grandfather@fda.hhs.gov.

As a reminder, GF products are not new tobacco products. So if you've modified your tobacco product since February 15th, 2007, and it's now a new tobacco product, you would need to

submit an SE report, SE exemption or PMTA instead.

All right. So when FDA receives a voluntary stand-alone GF request, we will review the information submitted to determine whether the product is a grandfather tobacco product. FDA recommends that you provide adequate information in your submission to assist in our review.

For example, your submission should include the following. One, the tobacco product name, again, as it was commercially marketed in the United States as of February 15th, 2007. And include a description of the tobacco product in your submission.

Two, test market information to help support that your product is a tobacco product that was not exclusively in test markets and that it was commercially marketed in the United States as of February 15th, 2007. This information is critical and we recommend that you include it in your submission.

And then three, adequate information to demonstrate that the tobacco product was commercially marketed, again other than exclusively in test markets, in the United States as of February 15th, 2007.

Now we'll review this information in more detail in the next few slides. I know everyone on our side cringes when they see light, but it's a good example for these purposes.

So tobacco product name, that's where we'll start. So one of the important key pieces of information in your submission is the exact name of the tobacco product. I've mentioned that three times now. It's just really important that we stick with the name as it was when it was marketed back in February of 2007.

So that's crucial. And the submission should include the full name so that includes both the brand name, sub-brand name, or any other parts of that product so we can, again, uniquely identify this product.

So here's the example. So if you --

on February 15th, 2007 had a product called Acme Light Hard Pack and you were commercially marketing these cigarettes in the U.S. by this name but later these same cigarettes were commercially marketed using just simply a different name, Acme Gold Hard Pack, the product name in your submission should be light, not gold. And throughout your submission you should refer to it as light not gold.

Now you could always drop a footnote and say hey, this product now is marketed as gold, but throughout, in all your linking information and everywhere you're talking about the product, please refer to it as the prior name that was used back in 2007.

The consistently cross -- that consistency across your documentation is really critical to ease the process of review for us. And, you know, to hasten, hopefully, the review of the submission.

So next we have tobacco product description. This is in additional piece of

information that is very important for us to help, again, identify this is unique tobacco products so we all know what we're talking about. So we recommend that you identify the tobacco products' characteristics.

For example, provide a description of the tobacco product which will allow FDA to review your submission and context, including a description of its components that comprise the product. A basic description of the materials. And how the product is used by consumers and include a legible photograph or schematic diagram of the tobacco product.

Please refer to our webinar again and guidance document which will include a lot of the information I'm covering today.

So on this slide is an example of a cigar product and examples of the characteristics that would help us to uniquely identify a cigar product, such as package type, quantity, length, diameter, tobacco cut size and flavor, or indication that it does not contain or

have a flavor.

If these characteristics are applicable to your cigar product, we encourage you to provide us with this information and any other characteristics for your product that uniquely identify it. These characteristics are especially important to help differentiate products with the same name, which we do see.

All right. Moving on to the second key component of your submission which is test marketing. This is used to help demonstrate that the tobacco product was not exclusively marketed in test markets as of the grandfather date.

When submitting your stand-alone GF submission, you may submit a test marketing statement. We have received statements from manufacturers with the following information. For example, the first -- first the statement should include the full name of the tobacco product under review, which matches the name identified in the submission and must be the name of the product as it was commercially marketed in

the United States as of February 15th, 2007.

My boss asked me if we had that in there enough times and I was like no, let's put it in one more time. So again, please use that name consistently.

Second, the statement should be from a responsible official. The responsible official should be an individual who has knowledge of the test marketing and commercial marketing status of the tobacco product on February 15th, 2007. And has the authority to make such a statement.

And third, the statement should be an affirmative statement confirming that the tobacco product under review was commercially marketed, other than exclusively in test markets, in the United States as of February 15th, 2007. That's important, affirmative statement. Please don't form it in the form of a question. We've gotten that before.

All right. So this is an example for you up here on this slide of a signed test marketing statement that contains the information

described in the previous slide. So as you can see, it's very simple, straightforward piece of information but it is crucial in our review, so we do ask that you please include it.

Okay. So the third key component of your submission is evidence of commercial marketing in the United States as of February 15th, 2007. On this slide I've listed some examples of documentation that you may include with your submission to help demonstrate the date of commercial marketing for your product.

You are not limited to these examples on this slide, but I do want to emphasize that the evidence you provide should be dated so that FDA is able to determine the date of when the product was commercially marketed in the United States based on the documents provided.

If you're unable to provide documentation specifically on February 15th, 2007, FDA suggests that you provide documentation of commercial marketing for a reasonable period of time before and after February 15th, 2007.

So for example, invoices dated February 13th, 2007 and February 17th, 2007. And again, please refer to the resources we have on FDA's website, guidance document, the webinar. Much of this information is in there and it will -- really facilitates your submission process.

So in addition to the records that we just showed on the last slide, FDA may accept other documentation that helps to collectively show that the tobacco product under review was commercially marketed in the United States on February 15th, 2007. These documents may include but are not limited to the items listed on the slide here.

Again, if you're unable to provide documentation specifically on February 15th, 2007, FDA suggests that you provide documentation of commercial marketing for a reasonable time period before and after the grandfather date.

All right. So on this slide you'll see some common examples of issues that would require FDA to send a request for information or

an RFI for short, based on our experience.

So the first one there, we've seen inconsistent naming of the product throughout the submission. Hence, why I'm really stressing please be consistent in what name you use for your product.

So for example, the product name on the invoice does not match the product that is the subject of the submission, so you called it X but in the invoice for the evidence that you're using to say that it was marketed on the grandfather date says Y, that needs to be accounted for in your submission. So it either has to match or you have to provide information as to how these are linked so we can have you address the discrepancy. Otherwise, we're going to have to request more information to suss that out.

Also, if you do find that a correction is made or needed to the name of your product, please make it throughout your submission so we don't create a new issue once it's corrected in

one place but not in others.

Okay. So the second one up there, we see an evidence provided that does not demonstrate commercial marketing of the tobacco product in the United States on February 15th, 2007. And third, we've seen situations where the collective evidence of commercial marketing, if we're in that scenario, in the United States before and after February 15th, 2007 is not adequate.

So what we recommend is that you review your evidence to ensure that the tobacco product name is accurate and consistently referenced throughout your submission. And the evidence that you provide supports commercial marketing of the tobacco product in the United States as of February 15th, 2007.

And again, I can't stress enough, please make use of the resources on our website, the guidance document, the webinar for grandfathered tobacco products. And please be on the lookout for any other materials that the

Agency puts forth in this regard.

Okay. So getting to the good stuff. Once you've done all that and it's all good and we've completed our review, FDA will notify the submitter of its final determination in writing.

So an example of a grandfather status determination letter appears here on this slide. The letter will state whether the product is considered GF. The GF status determination is based on the information provided in your submission.

Your review does not include a review of information concerning the composition, design or ingredients of the product in order to make the GF determination. But I do want to stress it is very important to include that product description information in your stand-alone submission.

Also, the determination only applies to the product that was commercially marketed in the U.S. as of February 15th, 2007. So again, harkening back to what I had mentioned before, if

you changed that product, it becomes a new product. To legally market it you have to come through another pathway.

And as -- let's see here, reminder, oh, I'm sorry. Remember that -- I'm sorry, I already said that. As you know, a tobacco product is eligible to serve as a predicate in a substantial equivalence submission. And so a couple things.

We do have all of our stand-alone grandfather submissions online in a database. It's available on our website. It doesn't list all grandfathered tobacco products that may have come in. So on our website we also include the substantial equivalence marketing orders which contain information on predicate products and they include other grandfathered status determinations.

Okay. So the not so good stuff. So let's say that you submitted everything and the determination was that we were unable to determine whether your product is grandfathered.

You would get a letter like this, as an example. And it would be stating just that. It would say that at the end of our review we have received insufficient information to make a grandfathered determination. And we will issue this letter to you.

Now a few things I want to stress. At any point during the process you may withdraw your submission. So if you're finding that through the course of our dialogue there might be some more things you have to gather, for example, you can withdraw your request at no penalty to you, and then come in at another time when you're ready, if that's what you want to choose to do.

Also I want to stress that if you don't do that and we do come to the end and find that we're unable to grandfather, you are allowed to come back in, there's no penalty, once you have gathered more, you want to go through the process again. The only difference is you'll be issued a new STN number for that product.

Okay. So as I stated, a grandfathered

tobacco product may be eligible to serve as a predicate product in a substantial equivalence submission.

So to put this into context, FDA reviews the SE report to determine if the new tobacco product is substantially equivalent to the predicate product and is in compliance with the requirements of the Federal Food, Drug and Cosmetic Act. When FDA's completed its review, FDA will communicate its decision in writing to the applicant.

Substantial equivalence means, with respect to the new tobacco product being compared to the predicate tobacco product, that FDA has found that the new tobacco product has the same characteristics of the predicate tobacco product or has different characteristics and the product does not raise different questions of public health.

And I'm sure Office of Science can let me know how I did on that little piece after. But, so now let's briefly review our process for

reviewing grandfathered tobacco products when used as a predicate tobacco product in SE submissions.

Okay. So when we review a grandfathered tobacco product referenced in an SE report, we use a similar review process used in our voluntary stand-alone GF reviews.

FDA may conduct one of two types of reviews when reviewing the grandfathered tobacco product, a cross-referenced review or a full review, as we term it. This will depend on whether the predicate product was -- had previously received a stand-alone grandfather status determination or not.

So the first, if the grandfather tobacco product receives a grandfathered status determination by FDA, we will conduct a cross-reference review. This means that FDA will review the information in the SE report and verify whether the tobacco product previously received the grandfathered status determination under the stand-alone GF review process.

In this case, the applicant should insure that the GF product referenced in their SE report actually received a GF status determination. And that the same information for the tobacco product is included as it was in the previously grandfathered stand-alone submission.

I'm going to repeat that one because it's really important and because I want to. So in this case, the application should insure that the GF product referenced in their SE report, one, actually received the GF status determination and two, that the information for the tobacco products is included as it was previously included in the grandfathered stand-alone submission.

Okay. I don't need to tell you, but I will. Those kinds of discrepancies can slow things down and create problems. So again, look back at what's been done, what was submitted and account for that and for future submissions going forward.

So secondly, if there's no reference

to a previous grandfather status determination, we'll conduct a full review of the predicate tobacco product which is similar to the review process for a stand-alone GF reviews. Since I've already reviewed our stand-alone GF reviews, I won't be reviewing that process again.

Okay. So that brings us to the end of my presentation. Here's a list of resources you can use to get more information on the topics we've just discussed. So please visit FDA's website at the grandfathered tobacco product webpage, second one down there. You'll find links to the guidance and the webinar that I've mentioned so much.

And then for questions regarding GFs, please use the email address listed there at the top there. The ctp-grandfather@fda.hhs.gov. And with that, this concludes my presentation. Thanks for your attention.

(Applause.)

DR. CECIL: All right. Well, thank you very much. I think it is now time to break

for lunch. We're right on time, believe it or not. We will restart up again at 12:30 and please enjoy your lunch. Thank you.

(Whereupon, the above-entitled matter went off the record at 11:27 a.m. and resumed at 12:32 p.m.)

DR. CECIL: Good afternoon. I think we would like to start this session because it sounds as if we're going to have an -- a potential extension. We're -- one of our goals with the afternoon, we've got two more talks, followed by two panel sessions.

And we will continue that second panel session until such time as we've answers the questions we have received. So we will have an expectation that that will go longer.

So for those of you who may need to leave at 3:30, that's fine, we understand getting to the airports from here is a non-trivial task. But we may extend well past the 3:30 timeline with the intention of getting to all the questions.

So, but we'll get to that when we get to it. Let's instead start, at this point, again talking about the scientific content. And we have two speakers talking about HPHC testing and reporting. Salome Bhagan and Melis Coraggio will be taking the next session. Thank you.

DR. BHAGAN: Good afternoon, I'm Salome Bhagan. I'm a chemist in the Division of Product Science in the Office of Science. This afternoon I'll present information on the SE scientific content.

This presentation -- I killed with the thing. This one, right?

(Laughter.)

MS. BHAGAN: Oh, okay. This presentation will provide a brief overview of the scientific review process. And then I'll discuss the data that may be considered when evaluating substantial equivalence based on tobacco product type.

I will also share examples of data tables that have facilitated FDA and their

reviews. I'll also share some common issues the different scientific disciplines have encountered in their review. The second part of this talk will be on HPHCs and that will be presented by Ms. Coraggio.

The examples in this presentation are based on our application review experience and the SE proposed rule. The SE proposed rule comment period closed on June 17, 2019. And so the SE final rule may change based on comments.

The information in this presentation may be useful for applicants because it reflects our current thinking based on our application review process and the SE final rule published on April 2nd, 2019.

As background, I'll share with you a brief overview of the SE scientific review process. As you may all be familiar with by now, the scientific review process is a collaborative review process performed by microbiology, toxicology, social science, engineering, chemistry, behavioral and clinical pharmacology

and environmental science.

During the time assigned for scientific review, there's a date set for a preliminary assessment meeting of the review team. This meeting further facilitates the collaborative review process. Typically, shortly thereafter, scientific reviews are finalized.

I'll now talk about the scientific contents in SE reports intended to demonstrate that a new tobacco product is substantially equivalent to a predicate product. The most common SE reports have been for the statutory products, cigarettes, smokeless products and roll your own products. Information about these products was presented in last year's public meeting and is available on our website.

The SE pathway may also be used for deemed products such as cigars, waterpipes and pipes. In this talk, I'll focus on the scientific content for SE reports for cigars, waterpipes and pipes.

Generally in SE reports, we receive

data on physical design parameters, tobacco blends, ingredients other than tobacco in the product, the stability of the product, harmful and potentially harmful constituents, referred to as HPHCs, and other studies which may include dissolution studies and nonclinical studies.

Next I'll give more specific examples of what this data may include for cigars, waterpipes and pipes. I'll distinguish this data based on scientific discipline, but there is overlap between disciplines as the review process is collaborative.

So first for cigars, they come in a wide variety of shapes and sizes and differ in the way someone may smoke them. But cigars are combusted products like cigarettes and so often the data considered for cigars may resemble that of a cigarette SE report. So here are the examples of types of data that we have seen for cigars.

Engineering has evaluated the design parameters for cigars which have included cigar

length, minimum diameter, maximum diameter, tobacco filler mass, tobacco raw density, tobacco moisture, tobacco cut size and wrapper porosity.

Chemistry has evaluated that tobaccos and ingredients in the cigar wrapper, binder and filler, which included a description of all the tobaccos and identification and quantification of all the ingredients. Chemistry has also evaluated information of HPHCs and will be further discussed later in this talk by Ms. Coraggio.

Microbiology has evaluated information on the container closure system and tobacco processing methods such as curing and fermentation which has included the description and process parameters for the tobacco processing methods.

Microbiology has also evaluated stability data, measured at time points post manufacture, which included water activity or moisture content, microbial counts and total yeast and mold counts, including tobacco specific

nitrosamines like NNN and NNK.

Toxicology has evaluated the changes between the new and predicate product and the impact of these changes on exposure. The rationales for these changes were supported by scientific literature and it is helpful when these references are provided in an appendix rather than in the body of the report.

To facilitate FDA's review of SE reports for pipes and waterpipes, the scientific content that is helpful is shown on this slide. Engineering could assess the design parameters which may include parameters such as hose or pipe length, hose or pipe internal diameter, hose or pipe permeability, stem length, bowl diameter, bowl volume, bowl shape, pressure drop and ventilation.

From a chemistry perspective, it would facilitate FDA's review of the tobacco blend and the ingredients other than tobacco in the tobacco product. And all the ingredients are fully identified and quantified. It may be helpful to

provide HPHC information to illustrate substantial equivalence of a new product to a predicate product. HPHC testing and reporting will be covered later in the second part of this talk.

From a microbiology perspective, it would facilitate FDA's review if information on the container closure system and tobacco processing methods such as curing, fermentation and heat treatments, including a description and processing parameters for the tobacco processing methods is provided.

Also, it would facilitate FDA's review if stability data measured at time points post manufacture is provided, including pH, water activity, nitrate, nitrite microbial counts TAMC and TYMC, NNN, NNK and total TSNAs. And a description of the stability testing condition which includes temperature and humidity.

From a toxicological perspective, it would facilitate FDA's review if the changes between the new and predicate tobacco product and

the impact of these changes on exposure is discussed as supported by scientific literature. It is helpful to the reviewer when the cited references are in an appendix rather than throughout the body of the report.

In the next few slides, I'll provide some examples of data presented in table format that we have seen in SE reports that have facilitated FDA's review. Here is an example table of design parameters that may facility FDA's review of cigars.

It's nice when the data's presented in this format showing a side by side comparison of design parameters for the new product next to the predicate product where the unit of measure comparing rod length, diameter, filler mass, rod density and rod moisture.

Next is an example table showing a comparison of tobacco blend between the new and predicate tobacco product. It has been helpful when the report provides a side by side listing of tobacco types and sub-types in a table which

also includes the units of measure, target values and ranges for each tobacco type, and a description of the tobacco grading system.

It's helpful to provide the amount of each component, for example, in reconstituted tobacco, in a separate table.

So next is an example of a summary of ingredient changes between the new and predicate tobacco product. It is helpful when the SE report contains a side by side comparison of the new and predicate tobacco product and provides information on the functions, components, CAS numbers and target values.

It's also helpful when the summary table is accompanied by a complete ingredient table showing all the ingredients in a side by side comparison for the new and predicate tobacco products.

Here is an example of a HPHC table. Ms. Coraggio will provide more information on HPHCs, but with regard to SE reports, it's helpful when an HPHC table like this one is

provided showing the smoking regimen, the HPHC and the measured values per units in a side by side comparison for the new and predicate tobacco products.

Next is an example of a table showing product stability. In a side by side comparison with the predicate and new tobacco product showing pH, moisture, water activity and relevant TSNAs over time. It is helpful when the data's presented in this way in an applicant's SE report.

Next, I'll share a few issues reviewers generally run into during evaluation of the SE report. A broader discussion of SE report issues was provided at last year's meeting and is available on our website.

From an engineering perspective, some of the commonly seen issues are that not all of the design parameters, target specifications and upper and lower range limits for the new and predicate tobacco products are provided.

There sometimes may be discrepancies

between the information provided by the applicants in the SE report and the data presented from the manufacturer.

For example, the data presented from the manufacturer in a certificate of analysis may differ from that in the SE report. And the SE report may list multiple or alternative materials for the predicate or new tobacco product.

From a chemistry perspective, the SE report may have incomplete ingredient information which may be missing ingredient functions or CAS numbers or the composition of complex ingredients may be missing. Sometimes ingredient changes may give rise to various HPHC concerns. And this information may be missing from the SE report.

From a microbiology perspective, the SE report may be missing or have incomplete stability data for the new or predicate tobacco product. It may lack information on specific time points or dates of the stability study.

There may be missing or inadequate justifications on the exclusion of attributes

that are likely to influence the microbiological stability of the product during storage in a stability study. And there may be inadequate justifications of established shelf life for the new and/or predicate products.

From a toxicology point of view, the reviewer tends to run into challenges with their SE report review when there may be a lack of adequate rationales and justifications why the changes to the new tobacco product do not cause the new product to raise different questions of public health. Or there may be a lack of bridging information or rationale showing the relevance of supporting literature to the new tobacco product in comparison to the predicate product.

I hope you found this information helpful in your effort to develop SE reports. And now I'm going to turn it over to my colleague, Ms. Coraggio, who will provide HPHC information. Thank you for your time.

(Applause.)

MS. CORAGGIO: Good afternoon. My name is Melis Coraggio and I'm a chemist within the Division of -- oops, sorry. There we go. Let's start over. I'm a chemist within the Division of Product Science under the Office of Science and the Center for Tobacco Products.

Today I will be discussing HPHC data and premarket applications. The content of this talk will focus on harmful and potentially harmful constituent data and premarket applications for both statutory and deemed products as well as the use and validation of methods to support reported HPHC data.

HPHCs are typically reported by any manufacturer or importer of a finished tobacco product. Applications are not expected to contain testing for all constituents on the established list of 93 HPHCs. However, FDA would like to see testing for HPHCs that are contained within or can be delivered by the type of product under review.

FDA suggests that certain HPHC yields

are measured in the smoke or aerosol for certain tobacco products under different smoke generating or aerosol generating conditions.

Additionally, it would facilitate FDA's review process for some products to report HPHCs measured in the tobacco filler or e-liquid. These particular measurements are suggested to evaluate how users may be exposed to different HPHCs during product use.

The tables on this slide represent matrices per product category for statutory products as well as deemed products in which FDA would like to see HPHCs reported to facility in our review process.

These listed HPHCs may be helpful to applicants in determining which HPHCs are appropriate for testing for each product type. Certain constituents have been selected as they represent a suggested group of several different chemical classes of HPHCs on the current established HPHC list.

FDA is currently seeking public

comment on the proposed list to add 19 constituents to the established list of HPHCs. This includes compounds such as polycyclic aromatic hydrocarbons, tobacco specific nitrosamines, carbonyl compounds, aromatic amines, metals and volatile organic compounds.

These are HPHCs we have seen based on characteristic changes, blend changes, ingredients. And here's some examples of HPHCs for cigarette and cigar smoke, smokeless tobacco, roll your own tobacco and product filler.

This slide is in continuation of the previous slide representing different chemical classes of HPHC for ENDS, aerosol, closed ENDS and closed e-liquids and open e-liquids. HPHC quantities typically are reported in the mass per unit of use where the unit of use is expected to be defined.

For example, in cigarettes, the -- in cigarettes the smoke yields would be reported in units per cigarette whereas a loose smokeless tobacco product would be reported in units per

mass of tobacco.

There are a number of internationally recognized smoking or aerosolization methods. Principally those methods recognized by the International Organization of Standardization or ISO, or the Cooperation Centre for Scientific Research Relative to Tobacco, CORESTA.

These smoking or aerosol generating regiments have been developed to evaluate how users may be exposed to different HPHCs during use. Here's a hypothetical data set for one cigarette brand and its predicate tobacco product.

FDA proposes that HPHCs in smoke for cigarettes be measured under both a non-intense, noted in this table as ISO3308, and an intense, noted in this table as ISO20788, smoking regimens.

For combusted and inhaled products, constituent yields reported under both smoking regimens help us to understand the way constituents delivered by a tobacco product can

change over a range of different smoking conditions.

It would facilitate in our review process to identify the smoking regimen, measurement units, mean quantities for both a new and predicate products as well as their standard deviations and number of replicates.

Furthermore, it would facilitate in FDA's review of the HPHCs in smoke for leaf or sheet wrap cigars be measured under internationally recognized standard cigar smoking conditions. This slide is a hypothetical data set of HPHCs in cigars. The tables note CORESTA recommended method number 64 is the smoking regimen used for the generation of HPHCs in cigar smoke yields.

The rows that contain N/A under the smoking regiment did not undergo a smoking procedure and are instead measurement of HPHCs in ground cigar, including the tobacco rod, binder and wrapper of the finished tobacco products. It would facilitate in the review process to define

N/A in your application.

HPHC reporting may be needed for both a substantial equivalence and premarket tobacco application pathways. In the instance of a premarket tobacco application, FDA also reviews HPHC yields.

In the case of ENDS, FDA suggests that aerosols for HPHC measurement be generated using an internationally recognized standard such as ISO20768. This test method is an example of an approach that may be applicable to your tobacco product. However, FDA does recognize that there may be other smoke or aerosolizing conditions that may be appropriate for HPHC generation.

As per the premarket tobacco application guidance for ENDS, if an alternative smoking or aerosol generating method is used, the applicant would be required to provide a complete description of the aerosol generating regiment used for the analytical testing, as well as an explanation to why the alternative provides comparable results to the intense and non-intense

smoking regimens that have been internationally developed.

This slide is a hypothetical data set of HPHCs for ENDS product. Again, the rows that contain N/A did not undergo an aerosol generating regiment and instead represent HPHCs measured in e-liquid.

So I'm going to switch a little bit topics here to method development and validation. Currently there is no CTP guidance on validation. Therefore, I will discuss validation in general that could be considered for validation of tobacco methodology.

Validation of verification studies are used in developing analytical methods to support regulatory submissions. This includes the analytical testing of the products, its constituents, ingredients, additives and stability testing of the finished products.

For the purpose of this presentation, method validation is defined as the process of demonstrating or confirming that the analytical

test method is suitable for its intended purpose. Validation applies to a specific laboratory for a specific product formulation and equipment performing the analytical test method for an intended use over a reasonable period of time.

Analytical method should be precise, accurate, selective and sensitive and the validation of a method should include measurements to demonstrate that all aspects of the validated method are suitable for its intended use. Appropriate reference materials should be selected for method development and validation that best represent the product undergoing HPHC testing.

In other words, validation should be conducted relative to a reference product with similar characteristics to the product undergoing testing. There are currently some reference materials available commercially for product testing. However, if a reference material is not commercially available, the reference material used in your method validation should represent

the product undergoing testing.

This slide represents the main factors used to determine whether a validating method is fit for its intended use. Accuracy is the closeness of mean test results obtained by the analytical method to the true value of the analyte. This aspect of the method determines the error in a measurement.

Precision is the closeness of an individual measurement of an analyte when the procedure is applied repeatedly to multiple aliquots of a single homogenous solution of an analyte. Precision approximates the indeterminate error in a measurement and is a combination of repeatability, intermediate precision, reproducibility and robustness.

Selectivity is the ability of an analytical method to differentiate and quantify the analyte of interest in the presence of other matrix components present in the sample. Selectivity is generally established at the limitative quantitation.

Sensitivity is determined by the magnitude of the signal produced by the analyte in the detector. This is the point at which the limited detection and limited quantitation are generally determined.

A validated method must be validated in the laboratory in which the testing is expected to take place. A validated method may be extended to other product formulations, different laboratories and across minor changes in equipment through a verification study.

Verification's typically done following a change to one of the procedures in a method or change in the product under test. The extent of the verification is dependent on the extent of the change. Verification demonstrates the laboratory's ability to successfully meet performance criteria that has been established in a previously validated analytical method with the changes incorporated. Any substantial change would result in a new method that would then need to be independently validated.

A few common issues FDA has seen with HPHC data reporting has been in the absence of deviations to a standardized method used in the analysis, the use of inappropriate reference standard during method development and inadequate number of replicates analyzed or any absence of critical validation parameters.

I'd like to thank you for attention and ask you please hold any questions for the panel following. Thank you.

(Applause.)

DR. CECIL: Thank you Salome and Melis, very nice. Our next, in fact our final presentation of the presentation -- for the final presentation of the day. There's the word I was looking for, the day, is the request for exemption from SE marketing pathways, given by Jennifer Schmitz and Matt Walters.

MS. SCHMITZ: Good afternoon. As Dr. Cecil said, I'm Jennifer Schmitz. I'm a Regulatory Health Project Manager within the Office of Science. I would also like to

introduce Dr. Matt Walters. He is the Deputy Director for the Division of Product Science with NCTP's Office of Science. And together we will be presenting on the request for exemption from substantial equivalence pathway, simply known as exemption requests.

So for this presentation we will be providing an overview of FDA statutory and regulatory authority for the exemption request pathway, the eligibility requirements for the pathway, an overview of the process and timeline, an explanation of how an exemption request is different from an SE report, the content to include with your exemption request and finally, exemption request metrics.

So let's began with a brief discussion of FDA statutory and regulatory authority for this pathway. FDA statutory authority for review of exemption requests comes from Section 905(j)(3)(A) of the FD&C Act. FDA's regulatory authority for exemption requests comes from first, the exemption rule under 21 CFR 1107.1

which became effective on August 4th, 2011.

Currently, exemption requests are the only marketing pathway with a rule in place. This rule established the procedures required to request an exemption and explains how FDA reviews requests for exemptions.

Second, as presented earlier, the Refuse To Accept or RTA rule under 21 CFR 1105.10, which became effective on January 30, 2017, applies to all tobacco product application types. This rule established when FDA would refuse to accept a tobacco product submission or application because the application has not met a minimum threshold for acceptability.

With an understanding of the statutory and regulatory requirements, how can a manufacturer determine if a tobacco product is eligible for an exemption request? In order to obtain a finding that a tobacco product is exempt from substantial equivalence, FDA must determine the following.

First, the new tobacco product is

modified by adding or deleting a tobacco additive or increasing or decreasing the quantity of an existing tobacco additive. Second, the proposed modification is minor and is to a legally marketed product. Third, an SE report is not necessary. And finally, an exemption is otherwise appropriate.

I would like to point out that for a tobacco product to be legally marketed, it should meet one of the following criteria. It is grandfathered, it has received an SE order, exempt order or a marketing order under PMTA or it is a provisional SE tobacco product which has not received a not substantially equivalent or NSE determination.

Now that we've discussed FDA authority and pathway eligibility, we can move forward with a brief overview of the exemption request and abbreviated report processes and timelines. Exemption requests require two phases of review prior to the marketing of a new tobacco product.

First, FDA reviews the exemption

request and if an exempt order is issued, the applicant submits an abbreviated report. Both of these processes are divided into three distinct phases: acceptance, notification and review.

For the exemption request pathway, we will focus on the acceptance phase as the notification and review phases are similar to the other marketing pathways. It is important to note here that exemption requests do not have a filing phase, as was presented in the PMTA presentation yesterday. The review process for abbreviated reports will be discussed in more detail as it is a unique process for exemption requests.

The Refuse To Accept procedures for premarket tobacco products submission rule was discussed during the PMTA presentation given by Ms. Emily Busta. For additional information about the Refuse to Accept Rule, please refer to the rule in the Federal Register. So for this presentation I will focus on the additional requirements for exemption requests.

Since some of the acceptance criteria is duplicative between the RTA rule and the exemption rule, I will focus this discussion on the additional criteria specific to exemption requests under 21 CFR 1107.1.

So in the first column of the table, we discuss the criteria specific for the format of an exemption request which should include first, that the application is legible. An application may not be legible if, for example, the application included scanned documents which did not transfer completely or have low resolution. And second, the application is submitted in an electronic format. As previously discussed under 21 CFR 1105.10, the RTA rule, submitting in an electronic format is optional.

However, under 21 CFR 1107.1, the exemptions rule, exemption requests and all information supporting the requests must be in an electronic format that FDA can process, review and archive. Electronic formats include submission through the CTP Portal, the Electronic

Submission Gateway or ESG, and physical media such as CDs, DVDs or hard drives. Please refer to the FDA website for additional information on electronic submission file formats and specifications.

In a situation where a manufacturer is unable to submit electronically, they may submit a written request to CTP which should include the following criteria. Explain in detail why they cannot submit the exemption request in an electronic format, request an alternative format and include an explanation why an alternative format is necessary. This request should be granted by FDA prior to submitting the exemption request application.

Oops, sorry, I went too far. In the second column of this table we will discuss what is needed regarding product information. First, the tobacco product can be legally marketed. Second, the proposed modifications are to tobacco additives. And additional information on tobacco additives will be presented later in this

presentation. Third, the applicant is also the manufacturer of the original product.

In the third column of the table we discuss what content should be included within the application. First, the manufacturer's contact information which should include the name of the manufacturer, the primary point of contact, the address and the phone number to receive any FDA correspondence.

Second, a rationale or explanation is beneficial to FDA to understand the purpose of the modification to the tobacco product, a description of the modification, why the manufacturer considers the modification to be minor and why the manufacturer considers that an SE report is not necessary for the tobacco product.

Third, a certification statement is a signed statement by a responsible official of the manufacturer which provides the rationale for the determination that the modification does not increase the tobacco product's appeal to or use

by minors, toxicity, addictiveness or abuse liability.

And fourth, as has been discussed previously, an environmental assessment or an EA in accordance with 21 CFR 2540.

So based upon OS experience in reviewing exemption requests for acceptance, the items listed here are the most common criteria missing when FDA refuses to accept a submission. As a reminder, if a manufacturer is unable to submit in an electronic format, they should request an alternative format as was previously discussed.

For tobacco product identification, it is beneficial to FDA to include this information in a readily identifiable table or section of the application. Finally, resources are available on the FDA website on requirements and recommendations for the creation of an EA. These resources include webinars, recordings of the 2018 public workshop and examples of EAs.

As we now have an understanding of the

acceptance process for exemption requests and the basic fundamentals of the review process, there is an additional step for a manufacturer to market the modified tobacco product under an exempt order, also known as the abbreviated report.

If FDA issues an exempt order letter for the new tobacco product under Section 905(j)(1)(A)(ii) of the FD&C Act, it requires that 90 days prior to the introduction or delivery for introduction of the modified tobacco product, the manufacturer shall submit a report, the abbreviated report, which will demonstrate the following.

That the product is in compliance with the Act. All modifications are covered by exemptions granted by FDA, meaning a found exempt order letter has been issued. The modifications are to a product that is commercially marketed and actions have been taken by the manufacturer to comply with the requirements under section 907, if applicable.

When an exempt letter is issued, FDA will provide an appendix at the end of the letter which will provide information on a format which may be useful when submitting the subsequent abbreviated report.

For the acceptance phase of the abbreviated report, FDA will do the following. After FDA has received and reviewed the abbreviated report, in general, FDA will issue an acknowledgement letter to the manufacturer. This letter acknowledges receipt so that manufacturers are aware of the 90 day timeline that must elapse prior to marketing.

For the review phase of the abbreviated report, FDA will conduct a review to ensure that all of the required information has been provided. And during this review, if FDA requires additional information, they will issue correspondence requesting the information from the manufacturer.

The final phase for abbreviated reports is when the 90 days have elapsed from FDA

receipt of the submission. If the manufacturer has received no additional correspondence from FDA within the 90 days, the manufacturer may market the new tobacco product within the United States.

So now that we have a basic understanding of the requirements to submit an exemption request and the subsequent abbreviated report, let's discuss some significant differences between the exemption request and SE report pathway.

There are key differences between an SE report and an exemption request which are important to note in this presentation. First, an SE report is comparing two products, a predicate product and a new product. For exemption requests, there is no comparison of products, as the request is to modify an original existing product.

Second, an applicant can use any tobacco product for a predicate in an SE report whether or not they manufacture or own that

product. For exemption requests, the applicant must be the manufacturer of the original and the new product.

Third, an applicant can only use a grandfathered provisional SE or previously found SE product as a predicate for an SE report. For exemption requests, applicants may request to modify a legally marketed product, including grandfathered, provisional SE and those previously found PMTA, SE or exempt.

So now I will turn it over to Dr. Walters, who will provide information on content to facilitate FDA review of exemption requests.

CDR WALTERS: Good afternoon. In submitting an exemption request, the modification of a tobacco product is limited to additive modifications only.

Here, on the screen is the statutory definition of an additive for your reference Generally, submissions are limited in nature and contain less scientific content as compared to an SUV port or a PTMA.

And past applications have generally been no more than 20 pages in length excluding the environmental assessment. To facilitate our view, FDA asks for these, this type of information.

A table identifying unique identifying properties of the new and original tobacco product, the product name, category, package type et cetera.

The eligibility of the original tobacco product, the grandfather status, previously filed SC, statement identifying the commercial eligibility of the original tobacco products.

And when you have information using a previously found SC or previously found EX used in a new X request as original tobacco product, information is stored that, that information is the same and/or identical.

Here's an example that queried identified as the unique identification of a new tobacco product and of the original tobacco

product that is being modified. These, this is a type of information that allows FDA to properly identify the new and original tobacco products.

Additionally, the unique ID properties for all tobacco products can be found within a memorandum on the FDA website. I refer to yesterday's presentation from Ms. Redus on the organization of our website.

I'm providing this as an example as many cigar manufacturers may not have experience with the unique identification. In this example for cigars, you will see that there are many properties that may differ to create a unique cigar product.

Therefore, in addition to the main properties for unique identification, which includes manufacturer name, tobacco product category, tobacco product sub-category, packaged type, packaged quantity, and characterizing flavor.

FDA also examines property such as length, diameter or the cigar, ventilation, and

the type of tip. These are specific to the sub-category listed. As the category and sub-category change, there may be more or less properties we look for from identification.

FDA has had quite a bit of experience with review and decision on exemption, decisions on exemption requests. Ms. Schmitz will cover some of these metrics later.

Based on this experience, FDA has found useful information which facilitates decision-making. For example, when FDA received the exemption request is helpful to be clear with the statement and purpose of the proposed modification.

Additionally, the final rule for exemption request requires that an applicant provide a description of the modification, so the FDA understands what's occurring. Additionally, the applicant must justify why the exception request is reasonable and why the SAB port is not necessary.

Finally, in applications requiring

agency action, requiring either environmental assessment or a valid claim and categorical exclusion. This can be found in a final rule of the RTA rule.

For exemption requests, FDA does not currently have a valid claim to calculate exclusion unless the EX request is being denied. Therefore, under 21 CFR 1107.1(b)(9) of the exemption request rule, the exemption request must include environmental assessment prepared in accordance with requirements of 21 CFR 24.40

As required by the final rule for the exemption request pathway, a statement of purpose for the proposed modification must be provided to facilitate understanding of the modification is beneficial for applicants to be clear.

For example, when providing the proposed minor modification, an applicant should state if it's either an addition, deletion, increase or decrease of existing tobacco additives.

If there are multiple increases,

decreases, additives or deletion the applicant should state those facts. If it is a substitution due to changes in suppliers, the applicant should be clear what additive, additives are being added and what additives are being deleted.

When describing a purpose, it facilitates our view to understand why this modification's being proposed. For example, is there a change in supplier to allow for multiple suppliers?

Is there an issue where a supplier's going out of business? Is there a new regulation that manufacturers must comply with? If yes, is it a State or Federal level or is it for another country?

Further, FDA has found from review experience that when manufacturers consider additional questions around their modifications and provide information to FDA, it reduces the need for clarifications and or deficiency letters.

For example, how does the proposed tobacco additive change impact performance or HPHCs? Are there any other changes? If so, is this appropriate for the exemption request pathway? Or is this something that may be more appropriate for the SC pathway?

Does the proposed modification alter your tobacco blend? For example, are you changing the percentage of bright and burley within your products?

If the answer is yes, this is outside the exemption request pathway and may want to consider an SU port or PMTA pathway instead. When describing the proposed modification did you discuss specifics about this modification?

For example, if changing an additive within your glue for your cigar, did you describe one, the absolute quantity? Meaning, you changed X microgram additive 1, 2, 3 to Y microgram additive 4, 5, 6 in the glue of the tip of the cigar.

Additionally, did you provide the

amount of the additive contained with the glue? Last, when looking at the example, the identification of supplier should provide, as well as the comparison of what is identical versus what is different between the additives.

Based on past review experience with the exemption request program to date, here are some examples of proposals that may be consider minor and inappropriate for this pathway.

I note that all these modifications are case specific or wanted to provide a general idea of some exemption request modifications that may be considered minor.

For the first bullet, we have seen change in additive source with a great impurity identical. This is commonly sense in cases when there's a change in supplier.

With changes that have been found exempt, applicants have a certificate analysis to demonstrate a change in grade and purity that are identical.

For the second bullet, we are looking

at a change in quantity of different additives that perform the same function. For example, consider sodium carbonate and potassium carbonate. Both of these are different molecules. However, they can perform the same function as PH modifiers.

When looking at potential changes to a container closure system, one example would be a change from a soft to hard pack in cigarettes. Having cases -- however, each case must be examined by some container closures may alter the characteristics such as a change from metal to plastic container in the smoker's product.

For examples, for changes in 9 FSC cigarette paper to FSC cigarette paper, this type of modification is expected to reduce household fires, a public health benefit. Even if they could, even if there is some slight increases in TNCO.

Additionally, manufacturers are often complying with U.S. mandates. The removal of complex additives often result in a decrease in

amount of additives added to a tobacco products, which would expected, reduce exposure to harmful chemicals for a consumer.

An applicant has demonstrated these modifications by providing a side-by-side comparison of the new and original tobacco products. We haven't seen examples of when an applicant changes the composition of a component.

For example, an applicant may change an additive composition of an adhesive between the new and original tobacco product resulting in minimal changes in the adhesive used in new and original tobacco product.

To contrast the last slide with examples of proposed modifications that may be minor. Here are examples of proposed modifications that may not be appropriate for the exemption request pathway.

When examining a proposed change to a design modification, there may be a significant change to a tobacco product's characteristics. For example, an applicant proposes to add a

filter to a non-filtered product.

This can lead to significant change to constituent's ingredients and potential consumer use of the tobacco product. Therefore, it may be a best interest for the applicant to consider alternative pathways.

As discussed earlier, changes to the tobacco plant itself is outside of this pathway. Therefore, this modification must be in addressed in SU port or PMTA.

When looking at potential changes to a container closer system a change in some container closes may alter the characteristics. As I mentioned previously, a change from metal to plastic container for a smoker's product. And this may not be appropriate for the EX pathway.

Finally, when there are a number of modifications that could impact a product performance, even if reviewed individually, when considered collectively FDA may determine that the collective modifications are not minor of a tobacco product and an SU port is needed.

Ms. Schmitz will conclude the presentation with overview exemption request. That's next.

MS. SCHMITZ: I need the clicker. Tag, I'm it. Okay. To ensure predictability, FDA has established performance measures for statutory products. These include cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco within the exemption request pathway.

Please note that FDA does not have time requirements for applications for deemed products. However, we will do our best to maintain these time lines were practical.

While we have just concluded fiscal year 2019, we still have open cohorts. Therefore, we intend to post all performance goals in January 2020 consistent with a timing in past years for performance goals.

However, I do still have some metrics of interest to share So, the metrics are broken into statutorily regulated products and deemed

products for both fiscal year 2019 and cumulatively.

This table provides metrics related to the exemption request pathway for statutorily regulated products for fiscal year 2019. As a reminder, fiscal year 2019 runs from October 1st, 2018 to September 30th, 2019.

So therefore as of September 30th, 2019, we have received 347 exemption requests, 85 of which are open within the FDA review process and 262 have closed.

This table provides the cumulative metrics related to exemption requests for statutorily regulated products. And again, cumulative numbers reflect all exemption requests received from the start of the center through September 30th, 2019.

CTP has received a total of 548 exemption requests for statutorily regulated products. Of those, 87 are still open within the FDA review process and 461 have been closed.

This table provides the recent metrics

for exemption requests for deemed products for fiscal year 2019. We have received 19 exemption requests, all of which have been closed.

Finally, this table provides cumulative metrics for exemption requests for deemed products. We have received 21 exemption requests, all of which have been closed.

So, this concludes the presentation on the requests for exemption from substantial equivalence pathway or exemption requests. Dr. Walters and I would like to thank you for your attention during our presentation.

We do recognize that a significant amount of information was provided. So, we do encourage you to ask questions during the panel discussion. Thank you.

DR. CECIL: Thank you, very much. All right and I think it is time to pull our hand list together. Can I ask our panelist to come up and find their seats? And one of them is running late, but that's okay. He'll be back. All right.

(Whereupon, the above-entitled matter went off the record at 1:24 p.m. and resumed at 1:25 p.m.)

DR. CECIL: All right. Let's go ahead and get started. Yes, I noticed that. I had not heard that yet. All right. But we will continue without Laurie for the time being and if she arrives, we'll let her introduce herself, so.

And our other individual will be back when he, when's he's back. So, let's go ahead and begin. Christopher if you would be willing to introduce yourself and have five minutes for a statement.

DR. JUNKER: Thank you. So, good afternoon. My name's Chris Junker, I'm Senior Director of the Smokeless Tobacco Products Emissions and Engagement Group at RAI Services Companies in the Scientific and Regulatory Affairs Department.

First off, want to thank the agency for this opportunity and this forum to have these discussions. I found that no matter how long

you've been in this world there's always some new bits of information that come out of these, these meetings.

Case in point is Ms. DeBerry's enlightening comment about --- sorry. The enlightening comment about the standardization of time between review cycles. That was certainly new information to me.

So, yes, always something to learn in these forums. I'll just say RAI and its operating companies have had extensive experience with the substantial equivalence process beginning in 2010 with the original SC reports on its provisional products.

Over the past four years, our understanding of the pre-market pathways has matured based on submission of various regular, regular SC reports and request for exemption from substantial equivalence.

Through this period, the form and content of our submissions under these two pathways has been matured based on learnings from

prior submissions and resulting inquiries from the Agency. And the evolution of the agency's positions on certain issues.

Given these experiences both positive and negative, I'd like to offer the following opinions. In the absence of foundational rulemaking that sets clear requirements for applications and metrics for their assessment, publicly available documentation from the Agency can be very informative.

As you've heard throughout these two days these things include marketing orders, TPL reviews, environmental assessments, policy memos stating the Agency's current thinking on a given topic, and the common issues, appendices that are attached to acceptance letters.

Though there's been some silence on what constitutes same versus different characteristics, this really leaves applicants with no choice but to look at a particular design parameter as either identical or different.

The agency has acknowledged the role

that different sources of variability play in the production of tobacco products. The topic continues to be a common issue underpinning deficiencies.

Therefore, applicants should ensure that study design, sampling, and analyses account for inherent sources of agricultural, manufacturing, and analytical variability.

Without some level of control for these confounding factors or an adequate description of their role in variability the Agency appears to judge any reported difference in data sets as directly related to design differences between the new and predicate products.

And finally, at the Agency request additional testing it is in the applicant's best interest to initiate the work with the standardization of review cycles and the time line for applicants to respond to deficiency letters there, there's really no or little opportunity for extensions to conduct testing.

So, at least in our opinion applicants can ill afford to waste that time debating the necessity of a given study. So, as stated previously, we did not come to these positions overnight. It is been essentially a decade-long journey that began with very little understanding of or guidance on the goal posts.

For the benefit of an audience with fast approaching compliance deadlines, I would implore the Agency to reach a consensus with the industry on its foundational role for substantial equivalence and to seriously consider the comments provided by RAIS to the proposed rule.

Specifically, meaningful definitions of and metrics for determining same characteristic, different characteristic, and different questions of public health are imperative.

It should be incumbent on the applicant to determine the most appropriate predicate tobacco product, regardless of product category or subcategory. Substantive criteria

that the Agency will apply when reviewing SE reports will greatly increase the quality of the applications that it receives.

And finally clear deadlines for the review of SE reports commensurate with the level of information required in Congress' intent for this pathway to be a streamlined approach to market will ensure that submissions are adjudicated quickly. So, thank you for your time and I look forward to the discussion.

MR. LONG: Good afternoon. I'm Gerald Long, Scientific Affairs Manager for ITG Brands supporting Tabacalera premium cigar division in regards to regulatory and marketing initiatives. Thank you very much for allowing me to serve on the panel this afternoon.

I believe that this type of forum is very valuable in helping both the agency and stakeholders develop an understanding of realistic expectations for the scientific content of submissions.

I'd like to briefly share some

experiences and observations on the topic of scientific content and evaluation of exemption request and SE reports specifically around supporting data.

Of course, when we talk about data for SE reports, we immediately think of HPHC data. But keep in mind that HPHC data are not mandated components of SE reports. FDA contends that it can use HPHC data as one of the metrics to determine if the subject of an SE submission is substantially equivalent to a predicate.

Of course, one challenges the criteria to use when comparing the data even in the case of cigarettes where analytical methods for the abbreviated HPHC list of compounds are relatively mature, sometimes these comparison criteria are not obvious.

The simplest approach of comparing new and predicate product HPHC data with TTAS is probably preferable in some cases. However, TTAS comparison of HPHC data have no provision for method capability considerations and could lead

one to incorrectly conclude that two products are different when they really are not.

If product comparisons require complex statistical analysis, one challenge the Agency faces is how to communicate product information such as HPHC data to consumers in a format that is both understandable and not misleading.

I'd like to focus several comments on scientific content and evaluation of leaf-wrap cigars, particularly, those described as premium cigars. We have collected -- excuse me.

We have collected data for the abbreviated HPHC list on 91 premium cigar products in 43 different sizes, 18 blends in both leaf and smoke. These data do not provide a useful metric for comparing products, these products for equivalency purposes.

We observe high variability in tobacco leaf HPHC results for the premium products that we tested. For example, the range of HPHC values in a single cigar blend were comparable to the ranges in HPHCs in the 18 different blends in our

study set.

So, in other words, the observed range for a given HPHC in a single blend was about the same as the range we observe for 18 different blends. However, select cigars with the same blend, had HPHC that were statistically, significantly different than other cigars in the same blend.

In those cases, statistical comparisons would conclude that those cigars have different characteristics based simply on a tobacco HPHCs when the cigars themselves, again, use the same tobacco blend.

We also collected data for the abbreviated HPHC list smoke and lights and observed similar confounding results. The main conclusion is that the resulting smoke HPHC data do not provide the ability to discriminate between premium handmade cigars.

The variabilities and fundamental design characteristics like cigar weight and pressure drop inherent to handmade cigars

directly influence the observed abilities in smoke HPHC deliveries.

The Agency should not follow the approach of allowable differences in HPHC results for cigarettes for the premium cigar category because there is high likelihood of erroneous conclusions in equivalence comparisons.

This is because HPHC results for premium cigars are confounded by the inherent variability of the cigar tobacco itself, variability in the product's handmade construction, the resulting variability of cigar-smoking results due to these factors along with yet uncharacterized variabilities in the cigar smoking methods themselves.

So, in summary, HPHC results are not viable metrics for distinguishing premium cigars from each other. Thank you.

DR. ROGERS: Good afternoon. I'm Colleen Rogers. I'm the Director of the Division of Products Science, which includes chemistry, engineering, and microbiology reviewers.

CDR WALTERS: I'm Commander Matt Walters. I'm the Deputy Director Division of Product Science and I oversee the chemists in the division.

MS. BELTRE: I'm Rosanna Beltre the Deputy Director for the Division of Regulatory Health Project Manager. I had a couple of comments. Not sure if you want me to do that now.

DR. CECIL: You're free to comment.

MS. BELTRE: Okay. Oh, sorry. I had a couple of comments that I wanted to go over that maybe we're not as explicit in the non-scientific presentations that we received today.

We've had a lot of good discussion sort of from the scientific perspective side and sometimes we overlook the really basic things that would make our life a whole lot easier.

So, I want to go over some highlights that, some take-home messages that were peppered throughout the presentations and maybe weren't as

clear for everyone.

Having good scientific data is, obviously, something that we like to see. Having service side-by-side comparison is definitely something that's very helpful and we've talked quite a bit about that.

But what we haven't sort of been very clear about is how you organize that information. Ms. Allard talked about having a nice table of content.

And even though the SE program, as an example, it's a program that's relatively mature, there are some things that we're still seeing that may slow down the review process before you even get to scientific review.

So, I'm just going to highlight a couple of things of, that are sort of low hangers that I think both CGP and industry could do a little bit better.

Nomenclature, labeling correctly, using table of contents, making sure that it's clear information that it's clear what the

information is for.

That it's well annotated, that your links are working correctly. Even with the SE program being really mature, we're still having a lot of issues around understanding why you submitted something or is a table superseding another table, duplication of data.

All these very small things collectively can cause the process to be very inefficient. And as the office is preparing to maybe receive a large volume of applications, we are evaluating all of those programs. We are evaluating all of our procedures and processes.

People that know me well in the office with tell you I'm the queen of process improvement. And I can only do that if people understand sort of what the pin points are. And I encourage all of you to really think about when you're preparing your submissions.

It may seem logical to you to organize it in a certain way, but I encourage you to think about Ms. Allard's presentation and making sure

that information is clear, concise, direct, well summarized.

Some things for instance that we see in terms of a acceptance and if we consider us receiving, you know, hundreds of thousands of application, Lauren DeBerry previously presented and talked about you know we'll try to get everyone through the acceptance phase. Right?

Well, it seems like a low hanger. We have some basic regulatory requirements to make it through the acceptance phase. And yet, we're still seeing, I'm getting caught up and trying to understand whether you met those basic requirements or not.

And if applications were better organized, we could quickly get through those applications. Get you through phase one so that then we can spend more time thinking about how to group these, these applications so that they could be ready for scientific review, which is where you want to be.

So, creating inefficiencies just like

on your end. We're definitely doing the best that we can. Our project managers, some of whom presented today, are also leading a lot of work groups thinking about, rethinking how we process our submissions and what we could be doing better.

So, if you have any feedback, whether it's either through questions for us or -- you can send them to your project manager as an end-user and it's someone who's communicating with us. I encourage you to please provide that feedback because it will help us in the future.

Let me see if I got everything. And the appendices, I think at the beginning of the panel you mentioned the appendices are provided in the acknowledgment letter and it might be a little too late because you've already assembled your application.

So waiting for your act letter may not be the best approach to putting together your application. So, I encourage you to monitor our website and to look at those appendices that are

posted on our website.

They're by product category and they will give you a better flavor of what the Agency's looking for and how to better organize your submission. And I'm done.

MS. STERNBERG: Hi, I'm Lori Sternberg. I'm Senior Regulatory Counsel in the Office of Compliance and Enforcement. And I am here not so much to convey information as to answer your questions.

In particular, my colleague Bryan gave us some information about the grandfather process, whether that be stand alone or as part of your SE application. And I'm looking forward to hearing your questions and concerns about that.

DR. CECIL: Thank you, very much. All right and we do have a number of questions. I spent some time trying to clump them all together into similar topics and there is not a replicate among them. So, there's lots of good questions here.

So, I'll start with the -- can CTP please explain when and how CTP determines if only one round of efficiency letters is appropriate versus two rounds of deficiency letters?

Some letters have the statement, we expect that no more deficiency letters will be issued for this application even if the letter was a first-round letter.

Some letters have the statement, we expect that no more deficiency letters will be issued for this application even if the letter was a first-round letter.

MS. BELTRE: Obviously, it's case-by-case. So, if the reviewers felt like they -- still? Sorry. Thank you. It's a case-by-case basis.

If the reviewers, when they conducted their first round of scientific review felt like they had enough information and that maybe the deficiencies that were provided were enough for them come to a determination that, that

information may be included.

It's not drastically different from the previous process where we have the PFind letter. And then, what we call an AI letter. The difference is now, like Laura mentioned, they're combined.

And if the technical Project Lead felt that we have substantial information in that first round of the review and maybe they're just a couple of more deficiencies that need to be resolved, they may include that information in the first deficiency letter that goes out to communicate that.

That doesn't mean that, you know, that's the end of it. It could -- did I cover that correctly? You guys would you like to add anything? No? Okay.

DR. CECIL: All right. Please, feel free to jump right in.

DR. JUNKER: I mean, I would, I would just to whoever said that, I would recommend that you reach out to your RHPM. Because, I mean,

they're -- it never hurts to confirm that, that is actually a preliminary finding and it's not something that fell through the cracks and should been an AI.

MS. BELTRE: Yes. I would add to that the RHPM's not serving just as the liaison to you they are also a liaison to the scientific review team. Right? So, they're in a very special place in my heart and in the review process. In that they do get to see sort of both sides.

And you know, if it was an error or if you know, whatever, the case may be, they're in a better position to maybe reach out to those reviewers and asked for a clarification and may be able to convey better where you are in the scientific review process.

DR. CECIL: Great. Thank you, very much. All right. Next question. Are the manufacturing requirements and inspections the same for PMTA and SE? Also, are the requirements for an environmental assessment the same for PMTA and SE?

Sure. Are the manufacturing requirements and inspections the same for PTMA and SE?

MS. STERNBERG: I'm not sure I'm clear on the question. But manufacturing requirements the same? Or inspections the same? Which did you say?

DR. CECIL: I, well perhaps if you could answer, are the manufacturing inspections the same? And as far manufacturing requirements go, I think, that is something the panel could to talk about separately.

MS. STERNBERG: Okay. Our inspections, application-based inspections are designed to verify the information contained in the application. So, no matter what the application is, we are looking to --

When we arrived on-site be able to verify the information you provided the agency, regardless of the pathway your application is going to take.

MS. BELTRE: I guess, I would, I would

clarify that in terms, for instance, where the SE and the exemption program, inspections are not necessarily a part of the review process.

But they definitely can happen by annual leave, which is, you know, some of the activities that the Office of Compliance and Enforcement. So, if there's some confusion there --

MS. STERNBERG: Right. That's part of why I was -- well a little difficult to answer the question. We don't routinely do an inspection for an SE application. But a manufacturer that has a product, that is marketed is open to its biennial inspection.

Any manufacturers that is registered and listing products is subject to the biennial inspection. Any application that is filed is then subject to verification on inspection. Those are two different types of inspection.

DR. ROGERS: Okay. And then, with regard to the EA, there should be no difference in the different pathways and that -- right, yes.

DR. CECIL: All right. And another question for OCE. What is the time line for voluntary grandfather review? I think that would be --

MS. STERNBERG: So, there's no statutory deadline for the, there's no -- the grandfather application process is voluntary and there's no statutory deadline for the review.

DR. CECIL: Thank you.

MS. BELTRE: However, I would like to put a plug that having your GF stand alone before you submit your application for a seat is really helpful. Having EORG after determination in advance of an SE application, it's really helpful.

MS. STERNBERG: It's a two part analysis. So, you can file for a stand-alone GF, in which case, the Agency will make a determination about whether it's able or not able to provide you with grandfather status or as part of your SE application, you can point to a predicate and ask for a grandfather determination

about that predicate. If you're going to do the later, then you just have to go through the first period of time to make that GF determination.

And then, the period of time to determine whether or not it's at SE. So, they each will take the time they will take. Whether it's Stand Alone for GF and then Stand Alone for SE. Or as part of a combined package. Does that make sense?

DR. CECIL: All right. Ms. DeBerry said that an applicant had to request FDA to begin review of a response for deficiency letter if submitted in less than a 180 days. This is new information. Could you expound?

MS. BELTRE: So, with revamping our letters, we wanted to make sure that communication was clear. And that any assumptions that were being made were clearly articulated in the letter.

So, the new language that Ms. DeBerry pointed out states that each cycle is 180 days and until that time lapses, at day 181 we will

initiate review. What we see is applicants submit partial amendments.

They may submit an amendment that responds to, let say, five deficiencies. They have five deficiencies, they respond to five. Because the time frame to respond is --

It's significantly longer. It may mean that additional testing was done. And we're still within the 180 day clock and they may want to amend and provide additional information.

So, to avoid sort of that piecemeal approach, we will wait the full time the applicant has to amend their application to ensure that we have a complete response. And we would kickoff review at day 181.

If an applicant feels very confident that they've responded to all the deficiencies in all of the requests and would like us to initiate review before our established time line, they need to adjust very clearly articulate that.

We are not going to assume that because there are four deficiencies and you

responded to four that therefore this is a complete response. So, it was just a way to just be clear about the expectations after deficiency letters are issued. And clearly, there's an Amber Alert.

DR. CECIL: Yes, another Amber Alert.

MS. BELTRE: Hopefully, they find what they're looking for.

DR. CECIL: I think, so. All right. Let me give one to Matt because we like to keep him on his toes. In the presentation on exemption pathways, removal of a complex ingredient was listed as a modification that may be considered minor. What about the addition of a complex ingredient or flavor?

CDR WALTERS: So, I think that would be a review issue that we'll have to evaluate in a submission. I mean, if it ends up beyond chemistry, we'll have to evaluate then. I think it's more of a review issue. Then -- do you need me to answer that right here?

DR. CECIL: I had another, I think

relatively straightforward. Of course, every time I say that they come out being very difficult. So, maybe this one will be too. Would adding a tobacco additive to a product that changes the characterizing flavor --- is it acceptable through the exemption pathway?

CDR WALTERS: Yes. I mean, I think it's a review issue. We'd have to evaluate that submission. I mean, in the examples that I provided of the cigar. I had cherry-to-cherry. And that was specific that it needs, it should be the same characterizing flavor.

DR. CECIL: There are a number of memos that have been posted on FDA's website. For the FDA, for all your own, the memo says that the quantity changes are no longer different questions of Public Health.

So, do we need to have a lengthy quantity change right up? Or can we cite the memo? It looks like, that it is unnecessary to work for the submitter and for the FDA reviewer.

DR. ROGERS: It is true that we have

a memo now, that lays out our current thinking about package quantity changes and the review process for FDA is fairly streamlined.

I think if the applicant decides to cite the memo and can explain why they feel that, that's adequate that they can do that.

DR. CECIL: Okay. Great. I'm trying to look, and I actually take one from online. In the panel discussion on PMTA review process yesterday, Christi Stark appeared to state that FDA would consider a new tobacco product authorized under a PMTA to be an acceptable predicate under the SE exemption pathway. Is our understanding accurate?

MS. BELTRE: Yes.

DR. CECIL: All right. For deemed products like pipes, there are no guidances available, yet. But I think I heard that the 2020 deadline is also applicable for these products.

How are we going to do the submissions? Is FDA planning to provide some

initial guidelines? That would be talking about future plans and whether or not we're not going to answer that question. But, how are we going to review these submissions?

DR. ROGERS: Well, the one comment I would make is that we did post on our website the appendices that we keep referring back to that are part of the acknowledgment letters.

So, those are a good thing to look at to give you a sense of the types of information that we're looking for the new products. As to how we're going to evaluate them, I can't really speak to that right now.

DR. CECIL: This one has to do with PMTA, but it will still apply. Would it an e-liquid manufacturer be expected to provide an analysis of the vapor and or aerosol output given the variety of device options and settings?

CDR WALTERS: So, knowing that there's a diversity of devices out there. And so, I think, if you justify the wires, so I think ace are in device to measure HPHCs in aerosol and in

an e-way grid.

That would be one way to justify why you choosing this device and how it represents exposure to this particular chemicals.

MS. BELTRE: I just wanted to make, I just wanted to make a clarifying point. We did talk about resources that we currently have online. For instance, the appendices we tried our best possible with the limited information that we have. Right?

At this time to put out some helpful information that may help people sort of think about information to contain in their applications. However, the list of memos, the last time I look at it, it was quite extensive and long.

So, in addition to having, encouraging people to read through them, I also encourage people to look at when these memos were written. They are written in one point in time, in a specific context.

And as we learn more about these

products. And as we receive more applications and gain more experience, that would sort of evolve.

So, yes, it's useful information. And yes, people should be referring to them, but definitely just be cognizant of, you know, how the limited use they could have moving forward.

DR. CECIL: And also, I just want to jump in a little bit on question about the e-liquid manufacturers. Keep in mind that there are a lot of different devices out there. And the ingredients that you put into your e-liquid when heated to an elevated temperature will degrade.

And your understanding of the degradation and the effects of those degradation products upon a user is going to be an important piece of information in your applications.

At this point, no, I'm not. Talking about -- sorry. To repeat the question, are, are we talking about a standardized device?

I do not believe that there is a final

standard device to work from. I'm speaking only of the temperatures that have been reported in the literature for the coil temperature that can go 400, 500, 600 degrees.

At some point, you do need to understand what the degradation pathways are for the components that you put into your e-liquids. All right. That one is a question for me. So, I'll put that one off.

If a statutorily regulated product was under scientific review, an AI request response submitted, or deficiency request, when CTP changed the deficiency letter will a PF letter be issued for that product?

MS. BELTRE: The new deficiency letter covers the language that -- so, let me step back. In the PFind letter, the original PFind letter and deficiency letter had two things that were different.

One, the time to respond. And two, it had some boilerplate language about this may be your last chance before we move forward to a

final action. That language has been carried over to the deficiency letter and where applicable it will be inserted in your letter.

So, if the question was, that in terms of the difference or you're still sort of going to get the warning, this may be your last chance even if it's a deficiency letter.

And because there's no longer a difference in time line that becomes mute across the two different letters. So, no more PFinds. I hope you all received a nice, fun, clean letter. And that you love it. And if you don't, that you tell us so that we can fix it.

DR. CECIL: Okay this is a long question, but I think it's quite a good one. Four, roll your own paper. Traditionally, we have HPHC testing performed on cigarettes that are made using the paper. We prevent access variability by putting tight limits on the RYO cigarettes.

For example, same type of tobacco. A certain amount of tobacco used, selected by a

pressure drop. Can also, only smoke by the CI method since they are wrapped weird. Have been asking the laboratory to double wrap the mouth end so that we have low variability.

But the manufacturer RYO, is very artificial. How do we connect the analytical data from this very artificial cigarette to questions of public health. And can we see analytical differences in our artificial cigarettes that are not, do not occur for smokers?

CDR WALTERS: So, make sure I understand. This is talking about how they would go smoking and roll your own tobacco, filler with fill-your-own paper?

DR. CECIL: Yes. This is for a -- I will interpret. So, for this, it's for a paper manufacturer, supposedly paper manufacturer. Is making test cigarette using a very consistent process by which to develop those cigarettes and smoking them.

But don't, do not necessarily

represent what the user might make. Is it still an important piece of information for FDA and even though they do not represent a market, likely outcome. And how are we going to evaluate those chemical differences?

CDR WALTERS: Yes. So, any smoking regiment is not a true representation of a consumer using that for a product. I do remember in our appendix we actually provide some suggestions.

In terms of how you may go about measuring certain HPHCs in the roll-your-own paper for select tobacco product filler, making sure that's consistent between a new and predicate product.

Between the two rolling papers, so that would be one. So, I would encourage you to look at the appendix because I know we weigh those for our companies.

DR. CECIL: And the follow up is actually a couple of questions, here, but we can combine them into one. Are cigarette paper

considered additives from the EX pathways perspective?

CDR WALTERS: Cigarette paper, yes, yes.

DR. CECIL: All right. That was two of those. That one we've covered. All right. This one might be for me too, so. If an e-liquid manufacturer uses only USP nicotine, does the manufacturer need to include a supplier of the nicotine?

If yes, does the application need to include samples made from both suppliers of nicotine USB? The same goes for PG and BG. Tagged.

The one thing I would say is that USP grade is a minimum standard. It does not say that this is, that they are identical. It just says you need me to be at least this good to be, consider your product USP.

And so, if you are changing your manufacturer, you would deal with it as if you are using any other manufacturer in a SU review.

If you are two different nicotines, we would need to look at those as different products or different components. Same with PG and BG.

I don't know yet. Let me come back to that one. Did I come close? Okay. I wanted to make sure. I'm trying to get some, one to get the panel, full panel involved rather than leaving this, you know, here. I've got one that can be messy. All right.

It appears to most of the industry including testing laboratories believe that requiring three batches and seven replicates for HPHC testing seems to be overkill. What would the industry say would be an appropriate number of batches considering the variability of the products? Okay.

DR. JUNKER: I appreciate that. I mean, I'll -- I really think it depends on how much variability you have in your product and your process.

What I would say is, is kind of what I said in my intro. I think the things that you

do to control for those factors can minimize the sample sizes you need.

So, if you're, you know, manufacturing these products on the same day, testing in the same lab, same equipment you know, for products that contain tobacco leaf.

If you're using similar or the same blend components pulled from similar sources of those tobaccos. So, so things -- there are things you can do to, that I think you can do, to minimize the sample sizes that you need.

MR. LONG: And I agree with Chris on that. And I would also say that, as we heard earlier today, is if the product is variable then the simple solution is just do more replicates.

I think the issue for the premium side of cigars would be that the product is inherently variable. And handmade nature of the product is essentially a characteristic of the product. So, I'm not quite sure where to go with this one.

DR. CECIL: Which is a fair question again taking at that next step. An inherently

variable product also has a variable level of risk associated with it.

And if you can help us identify a way to deal with that risk. Because if your one cigar is extremely high in HPHC and one's very low, there's a large variability certainly.

But we need to understand what the risk is to that end user to be able to determine whether or not these are substantially equivalent over, when comparing two of this, modified products.

MR. LONG: I would say again that right now where we are in this, the way it looks is, there's, there's so much overlap between the products that it's hard to really distinguish a difference between them.

So, you could almost argue that, you know, a cigar is kind of a cigar. Now, if you're talking about extremely small cigars to extremely large ones in smoke and light, you could argue that there are actual differences.

But in this middle ground of the

products that are primarily, that predominate the premium cigar market, they are almost indistinguishable based upon the results we're getting at this point.

DR. CECIL: All right. I will change the topic. I think there's more discussion certainly happening in the next section. I already queued one for the next section, so.

In the HPHC presentation, FDA indicated that non-intense and intense puffing regimens have been established for ends. FDA referenced an ISO method for the non-intense regimen.

Is that the same as the CORESTA recommended method? And what intense regime does FDA expect applicants to use for HPHC analysis of ends?

CDR WALTERS: So, the ISO method that was presented in based on the CORESTA method for ends. There is currently not any recognized methods, internationally-recognized methods for intense method for ends.

So, it would be suggested that if, to provide or document what intense regiment you are going to provide in your submission.

DR. CECIL: And keep in mind that the PMC, PMTA for ENDS guidance indicates that two different -- an intense and a non-intense testing protocol should be used. And that testing protocol does not simply mean puff protocol.

It also means temperature, potentially. It could mean different lengths of puffs. It could it end up being the number, changes in the variance or in your air flow through your ENDS device.

There a lot of different variables with an ENDS product that need to be defined. And you may use alternative approaches to dealing with an intense regiment, then simply changing the puffing protocol, like you do with a cigarette. And again, it would be up to you define what it is and what is appropriate.

All right we are almost at -- we've five more minutes left. So, for those on the

panel your time is almost done. Let me go back to our -- what exactly is required for an abbreviated report for exempt products? Is there a template or outline you all could provide?

MS. BELTRE: You will get an example in your exempt order letter. Is that --

DR. CECIL: Okay. That, that -- I

MS. BELTRE: What?

DR. CECIL: I was moving on to the next one. I'm sorry.

MS. BELTRE: Oh, okay. I didn't know if there was more to that.

DR. CECIL: If anybody is still confused, you can ask questions, ask CTP and we'll see what we can do there. Let's see, the AI and PF or PFind, deficiency letter, and there was a question as to what Ai and PFind are.

And so, I think they did want a clarification of what these things are and how they were used. Now, they've been replaced by a deficiency letter.

MS. BELTRE: Originally, we had a

advice/information request letter. We, I think in our last public meeting was our first sort of reiteration of clarifying the language and making it more plain, plain English and easier to understand.

It was sort of the first version of that process improvement. And as we evaluated all the letters, we started looking at making sure that things were labeled in a manner that they describe what was expected to be found.

Because advice/information, either your advising me of something, or you're requesting information, or are you doing both? And sometimes people would be confused by the title of the letter.

Sometimes, it would include requested information in those letters. Yet, when we talk publicly, we talk about deficiencies, and we talk about scientific deficiencies, administrative deficiencies. So, therefore we decided to change the name of the letter.

Acknowledgment letter is another one.

We're acknowledging receipt, but really were conducting a review to ensure that you meet regulatory requirements. And we're making a decision to accept your application.

So, that was another way that we felt like adjusting the language more articulated what the status of your application was versus the previous names of the letter didn't.

DR. CECIL: Let's see, as we have one more question, find a good one. Okay, Colleen, I'm sorry. What information specifically are you most interested in for stability studies for e-liquids.

The focus for smokeless was arguably microbial content. However, it could be argued through challenge studies that microbes cannot grow any liquids.

DR. ROGERS: Yes, so for e-liquids some of the things that we would be interested in would be PH, water activity. We would still be interested in looking at microbial content. I think challenge studies while they could be

submitted and could be used.

For challenge studies you would have to pick particular organisms for those. And if you were to do so, then you would have to explain why you picked the particular organisms that you did.

And then, depending on microbial content if any kind of microbial content was found, we might be interested in looking at endotoxin levels or aflatoxin levels to see if there's any of that present.

DR. CECIL: And I'll take up the one final question that was asked, had to do with analytical variability. There's actually several of them that speak to analytical variability.

And I think that we talked about it in the discussion of validation. And I think that the analytical methodology need to be clear to define.

When we're talking about variability, where is variability coming from? Is it coming from the analytical methodology? If it's a GC

mass spec, it's not likely coming from the GC mass spec.

It may be coming from the sampling process by which you either smoke your product or you aerosolize your ENDS product and collect it. And it is important to look at that level of variability.

And finally, it may be coming from your product. And if it is a product, it's important to identify that the product has variability that we need to understand and deal with. And I think that sort of information --

Inherently variable products are not necessarily the, a problem. We need to understand what it is. And understand what the effects of variable products are upon an SE application.

And that's -- we'll stop there. And say, thank you all. And before we release you all, I wanted to say, ask the audience to thank those who have spoken over the last two days.

And all of the panelists that have met

over the last couple of days for the all their time and concern. Thank you, so much.

We're going to take a 15-minute break and we will start off with the ask CTP leadership.

(Whereupon, the above-entitled matter went off the record at 2:16 p.m. and resumed at 2:41 p.m.)

MR. CECIL: Sorry for the delay. We have a few individuals that need to leave early due to issues of one type or another. And so we wanted to make sure we prioritized the questions for them early on so we can get them all in before kids have to be picked up or what have you.

All right. Could we go ahead and have everyone introduce themselves? Even though Crystal has introduced herself previously, there are new faces in the crowd, so --

MS. ALLARD: Sure. I'm Crystal Allard. I'm the Director of the Division of Regulatory Science Informatics in the Office of

Science at CTP.

That means that I primarily focus on providing IT solutions for reviewers and other folks in the Office of Science. And I'd like to take one minute to pontificate on something I heard yesterday.

MR. CECIL: Pont away.

MS. ALLARD: Okay. Thank you. I heard something in one of the panel discussions yesterday that struck me as really interesting, and as a great example of why we're here and what we're doing today.

I heard that there is a perspective that potentially FDA is consistently moving the bar or changing the goal post for industry. And I think that's really interesting.

From my perspective, we're incrementally trying to share as much information as we appropriately can with you in order to get to meet the bar, right?

And so I think it's really helpful to hear that when we share information, you're

receiving it and that you're digesting it and that you have questions and that you are asking, because we are trying very hard to give you the information that you need in order to understand how you can help us help you do a thorough and efficient review. Thanks.

MS. STARK: Hi, my name is Cristi Stark. I am the Director for the Division of Regulatory Project Management. You guys will be interacting with many of my staff.

You'll see their names, numbers, and email addresses at the bottoms of your letters. Please use your RHPM as your liaison for clarifying questions, for clarifications on the review process, or any other information that you are seeking. We will do our best to write it down and get back to you if we don't have an answer on the phone. Thanks.

MR. JONES: Hi, I'm Glen Jones. I'm Deputy Director for Regulatory Management in the Office of Science.

And following onto some of the

comments Crystal just made, we are here to really try to be as transparent as possible.

Some of the presenters today have talked about rulemaking that's out there, some of it still for public comment, guidance documents we've published.

But we also want to do webinars, do meetings like this to answer your questions, because we're really trying to give you as much information in a variety of different ways as possible.

MS. KABARIA: Good afternoon. My name is Swati Kabaria. I'm one of the Deputy Directors in the Office of Compliance and Enforcement here at CTP.

I apologize. I have a prior commitment at 3:15 so I have to leave around then. But if I don't get to some of the questions that you have for me, you can always submit questions to the Office of Small Business, which is housed in the Office of Compliance and Enforcement, and we will get back to you. Thank you.

DR. MURPHY: Hi, I'm Iilun Murphy. I'm the Director for the Division of Individual Health Science in the Office of Science, and we focus on looking at the health impact of various tobacco products.

MR. CECIL: All right. Thank you very much. Let's go ahead and jump right in. We're going to try and get through all of these, and see if we can make it happen.

So, first question. Is an importer of bundled cigars that package them in the U.S. be considered a manufacturer?

MS. KABARIA: I can take that. So if I'm understanding the question right, the bundled -- are the cigars bundled? If the cigars are bundled in the United States after they are imported, then yes, that entity would be a product manufacturer, tobacco product manufacturer.

If the products are bundled outside of the U.S. and then imported, that entity would be an importer.

MS. STARK: I'm going to add one note. Many of these definitions are actually derived from our statutes, so if you look in Section 900, you will actually see the definition of manufacturer.

Within manufacturer, you will see there are two subtypes. One is the classical definition of manufacturer, where you will actively make, package, label your product. The other is an importer, so there has been some confusion regarding is an importer a manufacturer or not.

I want to note that importers are defined under that manufacturer definition in Section 900 of the Federal Food, Drug, and Cosmetic Act.

MR. CECIL: All right. Once FDA issues a PMTA order for a product, would Section 301(tt) of the act prohibit the applicant from truthfully and accurately publicizing the FDA marketing authorization of the product, for example, via a press release or website

statement, even if the language used in the statement does not reference approval?

MS. KABARIA: So, Section 301(tt) of the Food, Drug, and Cosmetic Act prohibits statements that are directed to consumers that would mislead consumers that the product is approved or safe for consumer use or is endorsed by the FDA or is safer by a virtue of regulation by the FDA.

And we don't use the term approved when we're talking about authorizations of tobacco products. You can talk about your product as being authorized under the PMTA process, but 301(tt) would not prevent you from doing that.

MR. CECIL: All right. Where grandfather submission has been made but not yet determined, how should that submission be handled in the SE report?

Will the initial submission be reviewed, or does the new submission need to occur with the SE report?

MS. STARK: So I'm going to slightly reframe and just talk about some basic concepts. An SE report is one application type out of three to market a new tobacco product.

If a manufacturer is stating their product is grandfathered, meaning it was introduced or delivered per interstate commerce for commercial distribution in the United States on February 15th, 2007, that would not be something that requires any type of submission for a new product application.

This is part of the reason you've seen standalone voluntary grandfather determinations to help potentially if there are questions regarding that and to show evidence your product was out there.

If, however, you've modified that grandfathered product after that, and you're using that as a predicate, one of the things that would facilitate review during the SE review process is if you go through that standalone grandfather process first, have the evidence, and

then reference that STN as part of the SE report.

In the event that a manufacturer or an applicant has not yet done that, what will happen in the Office of Science is we will then send a request over to the Office of Compliance and Enforcement at the start of the SE review process stating, here's the predicate product, can you please take a look at the evidence and tell us, is it grandfathered or not.

MR. CECIL: All right. Great. The pile keeps growing while you're not looking. It's amazing. Tobacco Product Master File and grandfather products is the topic.

Could a Tobacco Product Master File be created for determined grandfathered products? This file would be referenced rather than submitting the previously submitted grandfather submission with the SE report, question mark. Can we just cross reference the GF STN?

MS. STARK: So as we discussed yesterday in the panels, the purpose of the Tobacco Product Master File is really when you

have information that you do not want the referencing applicant to look at, or for facilitating your review for multiple applications.

There was a question asked in the panel for putting an entire PMTA into a Tobacco Product Master File and we kind of beat around it, but we said there are certain things that don't really belong in the master file, such as samples.

Another example would be an environmental assessment, since that's for each product that's in there.

I'm going to look at a grandfather determination in the same manner. If you go through your voluntary submission and you receive a determination from the Office of Compliance and Enforcement that you are grandfathered, you'll see that there's a listing on the website that you could reference that you could place into your SE reports.

This is something that we're going to

allow for reference. You're not going to have all of the full materials in it. I want to note that the grandfather process, and I'll pass it over to Swati to discuss a little bit more, is through those STNs to allow for posting.

We will look at predicates, post that with part of our orders so people can see what they can reference. If it's part of the Tobacco Product Master File, people are not going to be aware of it, since those are protected. We do our best to have that firewall, again, for referencing.

So it's really in your best interest when you're looking at a grandfather type of submission to put that under a voluntary submission to the Office of Compliance and Enforcement.

MS. KABARIA: And I'll just add to that that the GF process through the Office of Compliance and Enforcement is merely a determination based on, you know, evidence that you submit, that your product was in fact on the

market as of February 15th, 2007, which is the grandfather date.

It doesn't include all of the detailed information that would be required for an SE determination, so that wouldn't be appropriate for a master file.

You would have to work with the Office of Science on the specifics of the requirements for SE to get the SE determination.

MR. CECIL: All right. This one was originally for Lillian, so what standards will be used for inspections for device manufacturers who frequently are only assemblers? How far down the supply chain will site inspections go?

MS. KABARIA: If this is in reference to a PMTA --

MR. CECIL: Yes.

MS. KABARIA: -- that's submitted, then we would be identifying the sites that we inspect through your application.

So you identify for us where your product is manufactured, and we would review and

determine which sites that we will visit as part of our PMTA review process. I'm sorry, I didn't get the other part of that question.

MR. CECIL: For device manufacturers who frequently are only assemblers for other parts that are received, how far down the supply chain do you need to go in your inspections?

MS. KABARIA: Well, that's going to be on a case by case basis. We review each application individually and we will review the information you submit and make a determination based on what you submit, where we will do our site manufacturing inspections.

MR. CECIL: Okay. A manufacturer has -- this is a hypothetical question, I imagine, a kit consisting of a closed tank containing an e-liquid and a proprietary battery.

They also sell a closed e-liquid tank and a battery separately. Crystal Stark stated the PMTA submission must contain the same subcategory. Would these products need to be filed under three separate filings?

MS. STARK: So we actually have a new motto. We're going to merge and become one character. You can see our names do merge to be Crystal Stark.

I'm going to start with identification of the products for submission, then I will turn it over to Crystal to talk about grouping for efficiency in an electronic submission format hopefully.

So when we're identifying products for potential authorization, we're looking at the actual product that a manufacturer is seeking. So what we're going to do is we're going to look at your battery that you're selling. We're going to look at your ENDS, your e-liquid in its closed cartridge.

Those two are going to be different products. They could be sold together. They could be sold independently. We're going to view it as, we're going to make a decision on those two, and if we say yes to those two, then it's going to be up to the company to determine how

they're going to package it and sell it out, but there's no need to submit it three different ways, each individually and then together.

When we're looking at the unique identification for these products, there are some questions, and this is where our project manager can come into aide for how you identify your product.

And when you go to look at our website for some of the policy memos, and I know Ms. Redus' talk also gave some websites where this unique ID memo is posted, you're going to see various categories and subcategories.

For some of these, it may not look reasonable to fill in the blanks. So if at all in doubt, you can call. You can always look at this as an ENDS component, but if you look at your battery, you're going to realize that there are other things that go into this, such as your watts or your amperes.

Give us that additional information, and then OS Can make a decision and a

determination for how that looks. You'll get that back in your acceptance letter from us if the application is accepted.

There's also the option to take a peek at some of the other items that have been placed on our website. We do try to update where applicable.

MS. ALLARD: Great. So when you're trying to determine what products you can group into a single submission to FDA, to CTP, there are four categories of information that we need you to consider.

The first one is, does it have the same manufacturer or importer? The second one is, is it the same application type? This means SE, PMTA.

And, pretend there are ands between all four of these, right, not ors, and is it the same product category, and is it the same product subcategory?

And when we say category and subcategory, we're very specifically referring to

the product ID memo. Commander Walters also mentioned it and included a link to it in his slides. I think it's in three separate slide decks.

You can also Google it. Google's really good at finding stuff. Google unique ID memo CTP, you will find it. If your products meet those four criteria, you can put them into a group submission.

I'm going to ask Todd a question. I know there was another question about grouping. Are we going to cover that later, or should I cover it now?

MR. CECIL: I'm not even sure where it is in the mélange here, so go ahead. Have at it now while you're thinking about it.

MS. ALLARD: Okay, great. So there were a couple of things about grouping that were asked in one of the questions.

One of them was, is there a limit to how many products you can group into a single submission, and the answer is no.

When we first started trying to do estimates for how many products we knew were on the market, and I'm looking at Swati because we looked at these numbers together, it's somewhere in the range of one to maybe 600 million products, okay?

And the idea of receiving all of those on the same day in May is terrifying for us. So if that means that we need to receive submissions with a very large number of products grouped by those four categories with the ands inserted in between them, we are prepared for that and our electronic systems will be ready to handle that.

One of the best ways that you can enable us to receive those is to take a look at the slides that I shared with the example spreadsheet. The spreadsheet that I've presented on my slides was only a screenshot. My apologies. I couldn't get all of the columns.

The second slide that I shared had, I don't know, 15 to 20 boxes. Each one of those boxes represents what could be a column in that

spreadsheet. If you provide that information to us for a large number of products, we will still be able to receive those and process them and review them. Thanks.

MS. STARK: So I'm going to use this opportunity for a little bit of discussion across the way here, when we're talking about electronic submissions and looking at very large numbers.

Well just look at ENDS liquids right now. And we're going to be all within the same manufacturer, same application pathway, we'll say PMTA, same category and same subcategory.

So I'm going to go with a closed e-liquid as an example. One of the other things I'm looking for is other types of things that you could submit electronically that would help facilitate FDA review.

I know that there are other items that we have out on our website, such as spreadsheets to assist with ingredient reporting that may be helpful. It may be helpful to know, I'm just looking at if there is UL certification, if

you're looking at your device or understanding coil temperatures if we're looking at that, if it's an entire closed system with a battery. I'm just looking at the options.

What are we willing to take here at FDA. Are we willing to take it all? Are you looking at test submissions where we could take a peek at this, or ways to have quick questions for child tamper resistance?

MS. ALLARD: Yes. So a lot of that information is helpful when supplied to us in a readily available electronic format, okay? So we are able to use that information and reuse it throughout the review when it's provided to us electronically in a format that we can read and review. Spreadsheets are good for that.

I would also say that I've received a couple of questions for a template for that spreadsheet and ideally, we would love to provide that at some point. Keep an eye on the website to see if we do, okay?

Just pay attention to what gets posted

on the website to see if we are able to provide more incremental helpful information about how you can provide us the information that we can use to review these types of submissions.

MR. JONES: I want to jump in at this point as well, because if you're going to, in fact, if you've got a large number of products, or even not so large, and if you're going to take advantage of that opportunity to group them together, Crystal has presented on the slide boxes that could represent columns of information to include.

But you could go beyond that depending upon what your product is and what type of information you're going to include in your application. You could, you know, put yourself in our position and think about what Crystal said in terms of the ability to take what's in the spreadsheet and use that to help the review team see what they're looking at.

So you could have columns for coil temperature and whether that coil temperature has

some type of a limit on it. You could have coil temps on there. Earlier in the day, I heard people talk about, you know, is the PG and the VG from a USB source? You could have a column in your spreadsheet that provides that information.

Earlier there were some comments about safety and product innovation and companies that might want to innovate with the products. You could have columns in your spreadsheet if, in fact, you have done innovation or you're, you know, if you have a flow restrictor, for example, you could have a column that makes it very easy for FDA to see up front that we put in place child resistant packaging or flow restrictors.

MR. CECIL: Swati, did you want to say something, or are you, all right. Good. All right. I have more questions. I was about to actually jump in and say let's go back to questions and make sure we get Swati out of here on time.

Okay. Another one for Lillian. If an unauthorized product is being sold on the market,

and the retailer is unaware that the product is unauthorized, can the retailer be penalized?

In other words, who bears responsibility, the retailer or the manufacturer, for unauthorized sales?

MS. KABARIA: Well, all of the above bear responsibility to ensure that they're in compliance with the requirements of the act. So the manufacturer bears responsibility in ensuring that they are not shipping adulterated or misbranded tobacco products into interstate commerce, and that includes products that don't have marketing authorization.

And the retailer bears responsibility to ensure that they're not selling misbranded or adulterated tobacco products. So I would say all of the above.

MR. CECIL: Okay, this one is a multi-part question, also for you. So I'll go one at a time. This is a fairly sizable chunk of text.

So would CTP consider the following new tobacco products requiring premarket review:

a filtered sheet wrapped combusted product that was commercially marketed prior to 2007, that has not been modified in any physical way, that was labeled as a cigar in 2007 and that was subsequently determined by a federal or state tax and authority to qualify as a cigarette and that is now labeled as a cigarette?

MS. KABARIA: So a grandfathered tobacco product is one that was on the market as of February 15, 2007, and I'm sure you all are aware of a recent court decision where the District Court of D.C. determined that modifications to the label of a tobacco product do not render it a new tobacco product if the contents within are unchanged.

So if your question is, the product itself is unchanged in any other way, then that product could qualify to be a grandfathered tobacco product, provided that you can submit that information when requesting that determination.

MR. CECIL: And would it be considered

to be a new tobacco product? Yes.

MS. STARK: I'm going to help with that, but with a little bit of clarification. So I want to note, when we're talking about the product, it's not just the physical product, it's also the container closure system around it.

So let me give you an example. I'll take a statutorily regulated product. So if you look at a pouched moist snuff, you're going to see that the container closure could be a tin. That tin could change from metal to plastic. That change in that metal to plastic, because it could impact characteristics, would render it to be a new tobacco product if it was modified after February 15th, 2007, in the United States.

The other thing I want to note is I do understand other agencies have definitions for how they label certain tobacco products and they differ from how FDA labels it.

What FDA is doing is we are viewing it based off of our definitions in our statutes. I can note that there are some differences when

we're looking at cigars versus roll your own.

So if you look at other agencies, they may look at the outer leaf when you're wrapping it and they may call that roll your own. When we're looking at our definitions here in our statute, that is going to be under the cigar category, not under the roll your own, because when we look at roll your own, we're looking at that final finished product going to the consumer and roll your own is following within that cigarette definition, which means it is wrapped in a substance not containing tobacco, which would automatically exclude that cigar leaf from that roll your own category.

So I want to make a note, even though other agencies may label something as a particular product, you need to pay attention to the categories here at FDA.

MR. CECIL: Okay. Next one. Okay. So now we have a tobacco filler product that was commercially marketed prior to 2007, has not been modified in any physical way, including

packaging.

Was labeled as pipe tobacco in 2007, has been determined since then to be called roll your own tobacco, and is now labeled as roll your own tobacco. Is that a new product?

MS. KABARIA: I think it would be a similar response, right? If the product itself has not been modified, if the container closure system, as Cristi correctly pointed out, has not been modified, if the contents within are exactly the same with no changes to the ingredients, the additives, the constituents, you know, what have you, then the product could, you know, qualify to be a grandfathered tobacco product.

MR. CECIL: I think the last one will fall in that same group. A tobacco filler product commercially marketed prior to 2007, not modified in any physical way, including packaging, was labeled as smoking tobacco suitable for use in a pipe or roll your own cigarette in 2007, and is now labeled as pipe tobacco.

MS. KABARIA: It's the same response.

MR. CECIL: All right. So that one was the last of the ones that have been identified as specifically and only for OCE.

There are others we would like your input on, but if you need to run, you're sort of off the hook-ish.

So let me jump to this one now. During the 10:45 session, and there's several, four of them, that have the same basic question, so I'll just read one of them.

Ms. DeBerry said that FDA is still considering comments on the proposed rule on the form and content of SE reports. Since the new SE report deadline is May 2020, six months away, will FDA be able to finalize the rule with enough time for us to follow it before the May 2020 deadline?

MR. JONES: Unfortunately, we don't know. We're working very hard on a variety of documents. As the administration mentioned a few weeks ago, we're working on getting out things in

compliance guidance.

We're anxious to also try to finalize the SE and PMTA guidance document and rules as soon as possible. But at this point, we do not have an estimate for when that will occur.

MR. CECIL: All right. I already know what this one's coming back to. What is the minimum concentration of concern for potential vapors generated by heating in combination with all flavor ingredients?

All right. This seems to be a question of what is a minimum safe quantity? It is going to depend dramatically upon the material itself. We know that changes in carbonyls like formaldehyde at a nanogram level can have toxicity issues as can a change in benzene or any -- so the appearance of HPHCs even at relatively low levels are of concern and are of a level that is consistent with cigarettes.

So I think that when we talk about, what is the concentration of concern, it really does depend upon which individual HPHC we're

talking about. And there are always going to be toxicity issues related with flavors also.

So unfortunately, I can't give you a hard number. It depends upon what it is. Things like acrolein are present in 16 micrograms per cigarette, in traditional cigarettes. We see formaldehyde present at low levels as about a hundred nanograms in some cigarettes. And there is concern with toxicity there.

So I think it is important that you understand what is present in your aerosolized e-liquid and that it is reported. We clearly do not want to chase zero. We aren't saying there should be zero of anything at this point. We just need to understand what is there so we can understand what are the implications upon the public health.

Okay. Ms. Allard's modules suggest that there are three and only three literature review sections, non-clinical, clinical, and population health, which includes epidemiology and modeling.

Is that true across the board, meaning that a single all-encompassing literature review is not acceptable, nor is a set of several literature reviews, each of which ties to several topics described in the proposed rule, such as toxicology, human health risks, human factors, et cetera.

MS. ALLARD: I'm going to address this from the perspective of the intent of the eTTD Table of Contents and not the specific question about the literature review, because it's true for all of the sections within the eTTD Table of Contents.

The eTTD Submission Table of Contents is written to provide a means for organizing submission information for all application types, and therefore it is the responsibility of the submitter to look at those sections and determine where their information is relevant and where it should be included.

It does not work the other way. You should not be looking at the Submission Table of

Contents and then be deciding what you need to submit. You need to decide what you would be submitting otherwise, and then use that Submission Table of Contents to organize the information that you would have included anyway.

So if you're looking at literature references and there are multiple places for you to put that information, you need to look at what you're including and determine the relevance to the particular eTTD sections that are available to you and determine what information goes where.

In general, when we're talking about electronic submissions, it becomes beneficial to you and to us to provide information in more granular, smaller pieces, rather than one really big document or what have you.

The smaller they are, the easier they are to break out, and the easier they are to digest and to link to and to bookmark and to work through and to assign and to move through our systems.

So if you're trying to determine

whether or not we want all information in one huge document, or you would rather break it down into relevant sections, in general it is helpful when you break things down into the relevant sections.

If you have questions about where things appropriately belong within that eTTD Submission Table of Contents, you can submit your question to the eSub help desk and we can help get an answer. We work very closely with the RPM group and with Cristi's folks and with the eSub help desk to make sure that we're providing those answers for folks. We're happy to help.

MR. CECIL: Okay. And this one is, I will paraphrase. With small companies that have only $1 to $2 million to spend, will they actually be able to submit PMTAs and remain on the market with only one or two products? And is this enough money to be able to achieve a PMTA for even one product?

DR. MURPHY: I see eyes coming towards me. So we recognize that there are practical

limitations to, you know, manufacturers and what they can spend on pursuing analytical studies, clinical studies.

So depending on what your product is, we've talked about telling the story, right? So I think of each of these application submissions as, like a book, right? And there are chapters you need to fill to tell the story of your product and then for us to conclude that the product is appropriate for the protection of public health, looking at the totality of evidence.

So some manufacturers are going to be able to submit bigger books, a lot more detail than others. But, you know, you can have a smaller book but it could still be of quality, right? So I think that it is a business determination to decide what is the information available to you that is publicly available, what can you bridge to, and what are the important areas that, you know, you want to focus on on developing your own studies to fill the gap and

to tell us, you know, the, kind of totality of the information about your product so that we can understand the potential impact of marketing this product to consumers and non-users.

MR. JONES: Yeah, as Iilun said, it's a business decision. It's not one we can really probably help you a tremendous amount with.

But in some of the earlier comments you heard me talking about the need to do long-term, long-range planning. And so I would encourage you to think not only about what products and what applications and pathways, but also think about the long-term plan in terms of post-marketing studies, post-marketing inspections, post-marketing reports, and all the responsibilities you have if you make a regulated product.

MR. CECIL: All right. This question, similar. Given the 2020 deadline, if a company has not yet started analytical testing, HBHC storage and stability, et cetera, how likely is it they will be able to submit an application

that would be accepted and filed by the FDA or CTP, by the May deadline?

MS. STARK: I'll start, and then I'm going to ask others to help join in. So there's really, when you're looking at the PMTAs, three phases.

I want to note acceptance, we went through the criteria yesterday and they were in Ms. Busta's slides. It's pretty small. We're really looking at identification of product, have you actually submitted your environmental assessment, are there a few other items that are outlined? We have that refuse to accept rule and then we have some of the basics for the PMTA.

None of the constituent testing really plays a part for an acceptance determination. When we get to the filing stage under 910(b), we are going to be looking at product characterization. Part of that, we are going to be looking at constituent testing with it, so I am going to encourage you to take a peek at some of the other applications that we have taken

action on, some of the TPL reviews and other items, to see where we're at.

And the same thing for the substantive review. If you have not yet started planning for testing, you need to do that immediately. Did I cut out? It sounds odd.

Product characterization is going to be essential. Part of what we're looking at for the product is what goes in and what comes out. Look to see what you can gather from literature, publicly available material, where you can bridge if you don't yet have it.

There are a lot of helpful items that were presented yesterday and today with that. So I don't think that it is a non-option if you haven't started, but you really do need to take a peek at that, look at all the content that has been presented, take a peek at some of the guidances that are out there, take a peek at the proposed rule.

Please comment on it just to get a sense of what FDA is currently thinking for a

successful application. And while you're at it, read some of the technical project lead reviews out there summarizing some of the PMTAs that have been authorized so you have a sense of how FDA is viewing that.

MR. CECIL: And I would also add that testing doesn't necessarily need to take a long time. It will benefit you if you find a friendly statistician that can help you identify how to do design of experiments, how many replicates need to be done, and make the decisions and provide the information on why you made the decisions you made.

And that will tremendously reduce the amount of work that you have to do and how much you have to spend. So I'm not a statistician by training but maybe I should be.

All right. Next question. Long question. How will CTP provide a path or an avenue for small businesses that operate adult-only establishments and have been operated for nearly a decade?

Thousands of smokers have qualitatively reported a healthier lifestyle due to changing from smoke to vapor. Let me get to the question.

Why is FDA asking each individual company to conduct its own scientific research and reinvent the wheel? There are four fundamental ingredients in e-liquids, PG, VG, nicotine, and flavor. Each of those ingredients already have studies of their own.

What is the likelihood that a PMTA for e-liquids is accepted, having cited the research results already conducted and including the additional literature with pros and cons to vaping as a smoking cessation alternative?

MR. JONES: Well, first of all, we're not asking people to reinvent what's already known, but we are asking people to submit applications for each individual product.

The question started talking about adult-only facilities, so from the retail perspective, the retailers have a choice. Maybe

they've been making their own product. They might continue to do so. If that's the case, they're going to need to go through one of the regulatory pathways for that product.

Obviously, retailers have other options, too, to partner up with someone who's going to be the manufacturer for the product that they're going to sell within their facility.

DR. MURPHY: I would add also that there are factors that impact health impact, right? So for example, if you use the same e-liquid in one device versus another, the aerosol content may be different, right?

Also, even for the, you know, a particular device, depending on the use behavior, the health impact might be different.

So I think that there are, you know, as Hans Rosenfeldt provided earlier, there is many lines of evidence that would help us understand, what is the product and how is it being used, to ultimately understand the impact on the consumer.

Because I think there is not just a simple, here is the e-liquid ingredients. Therefore, we should obviously be able to conclude what the impact on the individual will be, right?

There are a lot of different things to consider. So I think it's important for us to therefore be able to connect all the pieces together and again, I use the phrase totality of evidence to understand ultimately the impact of the product when it's marketed and used.

MS. STARK: I want to throw out one clarification as well. There was a term that was used in this question that actually does not fall under Chapter 9. That term was cessation. That actually falls to CDR, CVR, CDRH.

When you look at statements such as treat, mitigate, prevent, cure, treatment, those fall under the Safety and Efficacy realm, and they would therefore not be under Chapter 9 for tobacco products.

So we need to be careful with these

statements when we start to talk about cessation. This is something that we're going to look at from a jurisdictional process, and we're going to actually talk to CDRH or CDR or CVR appropriately for those sets of standards.

The other thing that I'm going to note, and maybe Todd can help a little bit since he is a chemist, is I know that everyone says there's only four ingredients, PG, VG, nicotine, and flavors. I want to note that there are differences with purity and grade for your PG and your VG.

There are different types of nicotine and flavors is many things. If you look at cherry, it could be 20 single ingredients, it could be 44 single ingredients, and depending on how it interacts with the container closure, leachables, everything else, you could be exposed to multiple items. So I want to note, it is not a simple four ingredients, if you'd like to add to that.

MR. CECIL: I think you said it

beautifully. There are not simply four ingredients. There can be as many as 50 or 100 ingredients in a given e-liquid.

All right. Next one. Make sure there was no other comments there. How will FDA deal with new technologies that represent significant advances in harmless reduction versus previously, and I've edited, products that have previously received marketing orders, e.g., a new technology that renders IQOS obsolete? I didn't write it.

MR. JONES: We certainly encourage the industry to innovate for the reasons stated in the question. The application review process should not be a barrier to that innovation.

We described over these two days, in fact, for example, with the PMTA, you can send in an e-Ask request. After that, if you're making a minor modification to additives, you can send in a new PMTA, which has less information in it by cross referencing the original PMTA.

So innovation is really critical to the industry and to CTP's mission to try to move

people to less harmful products. As I mentioned earlier, there's certain types of innovation that we're all aware of, the general public is aware of.

For example, with problems with e-cigarettes catching on fire and exploding. We would encourage you, if you have a question about moving from a product that was on the market in 2016 to one where you now want to have a UL or comparable battery standard, we would encourage you to reach out to the center, contact your RHPM, or send us a letter in terms of what you want to do so that we can try to work with you to get innovations such as battery standards in place.

Again, flow restrictors, other things you can do to address acute safety issues with the e-cigarette products.

DR. MURPHY: I wanted to add that we also have post-market reporting requirements that are attached to authorized products through the PMTA pathway.

And that also is another tool that allows us to understand that a product continues to be appropriate for the protection of public health. So, you know, as the marketplace evolves, we're able to monitor that.

MR. CECIL: All right. I have a whole bunch of questions from one person. I'm going to jump to somebody else's question and go back to them again. All right, are e-liquid containers required to have a specific resistance to impact, or will they be only required to be childproof?

DR. MURPHY: I'm not familiar with any requirements that we have for impact resistance. But again, whatever container shape or design, product characteristics you choose, then you should tell us your justification and rationale for choosing that container closure system.

And in terms of child protection, we recommend that it be child resistant. And again, there's more information on this in the ENDS final guidance.

MR. CECIL: There are regulations in

DOT dealing with packaging stability. So I think all of that is covered by other agencies beyond FDA. Okay.

If the language from the proposed rule goes into effect written as is, do you agree or disagree that abuse liability and topography studies would be required for ENDS PMTAs?

DR. MURPHY: Well, that falls under, you know, my division, so I like information on abuse liability and topography. I think they are very helpful. As I said earlier, I think that health impact is a compilation of many different things.

So how an individual perceives and, you know, the appeal and perception of a product impacts use behavior, use behavior impacts your actual exposure to the product, thereby, you know, causing, you know, downstream health effects.

So I think that, for me, understanding, you know, what the topography is, what the use behavior is of a product, and

understanding the abuse liability are important aspects. But as we mentioned earlier, the proposed rule is just that, it's proposed, and it's available for comment.

And if there are other ways that people think that information can be provided so that FDA has sufficient information to understand the ultimate impact of a product being used, whether it's by the consumers or non-users, then we will consider that.

MR. CECIL: Let me restate this one slightly. If open system products have been surveyed to be predominantly used by adults quitting smoking, and closed pod systems have been shown to be fueling the youth epidemic, is there a framework or guidance possible to strike the difference between open system flavored ENDS, which are helpful to adults, and closed systems, closed pod systems that are detrimental to the health? Paraphrased.

DR. MURPHY: So we don't have any policies about closed versus open system

considerations at this time. Again, whether you're an open system manufacturer or a closed system manufacturer, we're asking you to present, again, the information, all the aspects that have been outlined in the proposed rule as well as the ENDS final guidance for us to understand the potential impact.

Certainly, among those considerations is the impact on youth and impact on current smokers and other tobacco product users. So these are all considerations that we are interested in you addressing.

MR. CECIL: Okay. Will this process include products that do not contain nicotine and are not electronic devices such as flavored or flavorless non-nicotine liquids?

MS. STARK: So I'm going to reframe it a little bit with just the concept of what FDA is looking at here. We are looking at products that are defined to be tobacco products.

We're going to be looking at components and parts that, when assembled

together, would classify under that definition. So while you may be selling a device independent of your cartridges, if it could be linked up with a cartridge that contains nicotine derived from tobacco, even though you're selling that device separately, that would be a component for a tobacco product.

Therefore, that would require, if it's new, an application to come in and be authorized so that you could sell in the United States.

We have had cases where we strictly have received applications or inquiries on applications for products that are not to be sold with anything derived from nicotine.

So with those, we do utilize a jurisdiction group across FDA centers to verify if it falls under the definition for a tobacco product or not. If there is a question, we encourage you guys to ask up front.

Please do not just assume, because you could very well have a component that is a tobacco product that would require you to follow

through the regulatory process as appropriate.

MR. CECIL: How will FDA consistently elevate newly deemed ENDS devices against the benchmark of APPH?

DR. MURPHY: Continue to elevate the benchmark?

MR. CECIL: Is that what, how will FDA consistently evaluate newly deemed ENDS devices. Sorry.

DR. MURPHY: Okay. Evaluate how we --

MR. CECIL: Sorry.

DR. MURPHY: -- consistently. Okay, well, we have one office director, Office of Science Director, who is currently the only signatory for the PMTA submissions.

So by nature of that process, there is consistency as best possible through, you know, making decisions. We do have a team of project leads that do the scientific evaluation of these applications.

And we do talk constantly and we do meet regularly to assess kind of the content of

these applications and trying to understand what the balance is in looking at the information to make the scientific determination that a product is appropriate for the protection of public health.

So I think that there are internal measures in place to try to be as consistent as possible across the scientific teams that come together.

MR. CECIL: If a major amendment to a PMTA is triggered due to the submission of additional final data from a clinical slash lab test, would this require the product to be pulled from the market if it is after the May 12th, 2020 deadline?

MS. STARK: I'll start with this one. So when we're looking at the May 12th, 2020, deadline, what we're going to be looking at, first pass, is I'm going to be looking to see what have we received?

Did we receive it by 11:59:59 that night? Hopefully across portal, because we want

it to be electronic. She's smiling. If the answer is no, then we already know that those products would require prior authorization.

They shouldn't be marketed. If, however, we have received it, the applications have not received a refuse to accept or a refuse to file and later on there's a major amendment, we're looking in that one-year process right now and there hasn't been any type of negative action for them to come off the market.

If, however, we get to May 12th, 2021, we're going to have to talk about those cases at that point in time to see where are we with the review? What is it looking like?

This is where there may be some follow up with your regulatory health project manager with the status. I am pretty sure there will be some communication from the center regarding that, but we're going to have to look at those cases as we get there.

There is a large difference in what we consider major amendments. If we're getting a

major amendment for a brand new study with pivotal endpoints because nothing was submitted originally in the application, that may not be the best contender for us to look at in that case by case.

If, however, it may be something else to support some questions that FDA may have issued in a deficiency letter, that may be a different case. So we will have to look to make sure, one, do we have an active application in house, and two, where are we with the application and the contents within?

MR. CECIL: Okay. Again, I'll paraphrase this one. So if FDA banned e-liquids, it is very easy to make your own with PG, VG, and your own flavors and nicotine. How will FDA regulate this?

MR. JONES: FDA has not announced any plan to ban e-liquids, so I think the question is moot.

MR. CECIL: Okay. We may have actually covered this before. Assuming 400,000

SKUs get RTAs, how long after that date or the compliance deadline do retailers have to clear stock now slated for removal from the market?

MS. STARK: So Swati has unfortunately left due to other obligations. I'm going to note that when we're looking at the deadlines here, this goes to some of my past comments.

We're going to be looking, did we receive the applications by May 12th, 2020? After that date, we're looking to see, is there any type of negative action? One of those could be a refusal to accept. If that occurs after that date, those products no longer have an application in place. They are not taking advantage of those compliance policies.

There will be instructions associated with the letters. There should be communication coming out of CTP. And the Office of Compliance and Enforcement will assist with what we need to handle for any type of potential enforcement or other actions related to those products on the market with manufacturers and with retailers.

So if this isn't the answer that you're looking for, which it may not be, please resubmit it through our Ask CTP so that we can make sure that our colleagues in the Office of Compliance and Enforcement can provide a little bit more detail to respond.

MR. CECIL: Okay. Product characterization includes manufacturing practices. So, one, how does the applicant resolve the disconnects of the lack of GMPs or TPMPs, and two, resolve the disconnect of providing this information for products not on the market? I can try.

How does an applicant resolve the disconnect of the lack of GMPs or TPMPs, and resolve the disconnect of providing this information for products that are not on the market?

MR. JONES: I think there may be a point of confusion here. As you saw in some of the presentations earlier today, manufacturing practices, processes, validation, and consistency

is very critical piece of the product review, PMTA review process.

And so it's important for you to demonstrate through your application that you do have a controlled process for manufacturing.

The agency at some point will probably put in place TPMPs, Tobacco Product Manufacturing Practices. Those would be requirements that would apply to manufacturers of all products, including, for example, grandfathered products.

But the absence of those regulations or requirements at this time doesn't eliminate what a company needs to do if they're pursuing a product through the PMTA pathway.

MR. CECIL: Okay. I agree a hundred percent, by the way.

MS. STARK: I like to think of it in terms of a big picture concept. When we're thinking about a PMTA here, we're looking at, and Dr. Benson gets the credit for this, and Todd, I know that you stated it earlier. Tell us your story.

Part of that story includes how you make your product, your recipes, how you ensure it is the same product coming off the line, what's your target value, what are your specifications?

If you don't have this, or if we're starting to see information that's far outside of it, that may not be the same product, and that's really what we're asking for.

TPMPs, you look at GMPs and other centers. They help to get that consistency, that accuracy when it's coming across, but that's still part of your story to make sure right now when you're making that product the same thing that you intend to be sold to consumers is what's coming off your line. And that's really what we're looking for in these applications.

MR. CECIL: Upon submission of a PMTA or SE application for a deemed product, will FDA inquire whether the product is currently on the market and or request certification or documentation of the 8/8/16 marketing of the product?

MS. STARK: So I want to note for the compliance policy of August 8th, 2016, that is particular for products that currently require premarket authorization, that they can be marketed under this compliance policy if they follow certain items.

I want to note that this person asking the question might have some experience with provisional products where it was slightly different. So I'm going to kind of walk through a couple of definitions.

A provisional product was a tobacco product that was on the market. It's a new tobacco product, so it was in the U.S. after 2/15/07, and an SE report was submitted by 3/21/2011.

For those products, they are allowed to legally be marketed unless they receive an order that they were found not substantially equivalent. That's a little bit different than these deemed products under compliance policy, because these are not legally marketed. We just

have them marketed under the compliance policy.

With the provisional products, FDA went through a series of questions to verify that they truly were provisional, to make sure that we understood if they were legally marketed or not, because as we were going through the application process, we had to understand how to handle, when to post various other items associated with it.

With respect to the deemed products, there may be similar questions in the future depending on where we go and some of the notifications that we have to give to the public.

I want to note that in addition to any type of clarifying questions that may occur regarding products being on the market on 8/8/2016, FDA may inquire for that through inspections.

So it may not be something formally coming from the Office of Science. It may be if you have individuals from the Office of Regulatory Affairs in tandem with Compliance and Enforcement and OS staff, out there for PMTA

inspection, during the inspection they may actually ask, can I see some of your evidence that your product was out there on this date?

So I just want to make sure people are aware that you may be asked at different points in time. In addition during that, they may ask for other types of regulatory requirements.

I want to note one of the other ones, and I mentioned it yesterday, was the requirement to submit ingredient listings. That applies for both foreign and domestic.

So please be aware of all regulatory responsibilities. Know that as manufacturers, you're required to comply with them and you may be asked at different points in time, so stay tuned.

MR. CECIL: All right. I want to modify this one a little bit, even though I think I know what the author was asking for.

So I have a cigar product, premium cigar, that's manufactured, is GF eligible, and I switched my source of tobacco from a field in

Virginia to a field in North Carolina. I made no other changes to my product. What is required for submission on May 2020?

MS. STARK: I will start and then I'm going to ask Todd, since you're our chemist, to assist. When we're looking at if you're a new tobacco product or not, I'm going to look at, have you modified your product?

And the short answer is, if you have not modified your product, then you could maintain your GF status. You have that GF status, but you would not be required to have an application.

The question is getting down to the tobacco itself, if that has changed. So there may be different types of tobacco, and I'm going to ask, phone a friend, I'm going to go to a chemist, since I'm not a chemist, to ask that.

But I'll make it really simple. I may change my tobacco itself. Let's just say that my leaf, I'll make it really easy. I'm going to change from burley to bright. That's a different

tobacco. That's a modification. That's a new product. I'm going to ask if you could help clarify a little bit further with this one for cigars.

MR. CECIL: We have not, to my knowledge, differentiated field to field, country to country, source to source, of tobacco leaves.

So a burley tobacco for the purposes of SE and PMT review, is a burley tobacco. A bright tobacco is a bright tobacco. So hopefully there's few changes being made to premium cigars.

Next question. All right. This is a slight deviation from that previous question. Child-resistant packaging.

It seems clear that open ENDS liquids would need to demonstrate child-resistant packaging. However, what about closed ENDS cartridges? Would they need to show child-resistant packaging? And what about pods?

MR. JONES: The issue here is acute nicotine toxicity, and so even with closed systems, there can be, and we've seen experience

with, leakage from some of those systems, including pods.

So the burden's really on the applicant to address the issue of nicotine, acute nicotine toxicity. And again, I'll go back to the issue of post-marketing.

It's probably better off, generally, if a manufacturer tries to anticipate problems rather than wait until after they've submitted the application and get it on the market and then face consequences such as recalls, vials breaking.

I know earlier there was a question about the glass and so forth. So this goes to good quality control and testing and making sure you have a robust product that's not going to subject users to nicotine leakage or other exposure.

MR. CECIL: Okay. I'm a manufacturer of cigar wraps. I sterilize them and I package them for sale. If my GF determination application is unsuccessful, how do I market my

product?

MS. STARK: So I just want to note that a standalone GF submission is voluntary. Part of the benefit for submitting it is making sure that you have the evidence and that you have a letter back from the Office of Compliance and Enforcement that you are grandfathered, because that's something easy to show if you have an inspection, that you have a product that can be legally marketed.

Otherwise, they may be asking for evidence to show that this is grandfathered. So I just want to keep that in mind. A standalone GF submission is not required. If the product is GF and you are complying with all of the other regulatory requirements, you should still be able to legally market your product.

If, however, you do not have the evidence and there's information to believe you have modified it since it's a new product and you do not have an order, you could be in violation of the act.

MR. CECIL: Okay. This one is a slighted change in tone, which is fun. There are a lot of great questions raised at this meeting. Will you be posting answers to those on your website, including the questions that you've not had time to answer today? That's it.

MR. JONES: So I think we're going to have a transcript of this session on the website. The slides will be posted. I think we're trying to answer all or most of the questions today.

But you can continue to send in questions including to Ask CTP. We will look into the possibility of over time developing some perhaps Qs and As or something to post on the website.

MR. CECIL: Thank you. Okay. Could a cigar product on the market as of February 15th, 2007, that has only replaced the filler tobacco because it is no longer grown or available anywhere in the world, obtain GF status? Would it be exempt from SE?

MS. STARK: Okay, so if you modify

your product after February 15th, 2007, you're changing your blend, you're changing your percentages of your tobacco in there, that would be a new tobacco product.

The second question is, if you're changing the filler, could you go down the exempt from SE, that exemption request pathway, and the answer is no.

The exemption pathway is strictly for the addition, deletion, the increase or decrease of a tobacco additive. Tobacco itself does not work in that pathway, so you would need to look at either an SE report pathway or a PMTA.

If you have a grandfathered product, that would be a nice predicate to look at for the SE report itself. If you do not, then your other option is going to be a PMTA.

MR. CECIL: Which I think actually comes to this, the follow up question, which is, if the product receives a marketing order and the tobacco needs to be replaced in the future for the same reason, what should be done?

MS. STARK: So if we receive a marketing order, it's going to depend on what the order is for the appropriate pathway. And I'm going to just kind of repeat some basics so people have an idea, since there is three pathways to market.

You have the PMTA pathway, where you don't need any predicate. If you're authorized through the PMTA pathway and it's something that's minor, we can look at a supplemental PMTA, where you would cross reference and provide that bit of information in for determination from FDA.

If you have been authorized under the PMTA pathway, you are not eligible to go and use the SE pathway. That's because SE has a requirement with the predicate, it's either grandfathered or previously found SE.

You do have an option to utilize the exemption request pathway if you're making an additive change that is minor. So if you're changing the tobacco filler itself, that would not be appropriate for the exemption request

pathway.

When looking at the exemption request pathway, you can modify any legally marketed product. So that means you could modify something that was previously found exempt, where you've actually submitted your abbreviated report and placed it out there. You could modify something previously found SE. You could modify a pending provisional application, one that FDA hasn't reached a decision on and hasn't been found NOC. You could modify something authorized through the PMTA, as long as it is that additive change that's minor.

So again, tobacco itself is not going to be part of that pathway. For SE, you have two options for predicates. Your predicate is either going to be one that is grandfathered or one that was previously found SE.

think I hit all of them. Did I hit them all? Yes? Okay.

MR. CECIL: All right. I have a couple of connected questions here. We have some

roll your own related products that do not really fit into any other roll your own subcategories.

One, how do we categorize them? So far we've tried to find the best fit category. And two, what do we do if we don't agree with the category FDA has assigned the product? I'm mostly worried that we don't provide the necessary information if we categorize differently than the FDA.

Also, would there be an option to add a category, or should we utilize the Other category?

MS. STARK: Okay. I'll hit this, because this hits some of the earlier comments. I want to make sure that when we're looking at categorization, we're actually looking at the definitions from FDA and not from other agencies.

So when we're looking at the roll your own definition, I need to ensure that people are going to Section 900 of the FD&C Act and ensuring that it's appropriate. If they have questions, they can look at the policy memo online regarding

unique ID. They can also call a regulatory health product manager.

The one example that I gave earlier around a cigar leaf, that does not fall within the roll your own category. Roll your own is a statutorily regulated product category, and that is where we're looking at a final definition of cigarettes, where it is tobacco rolled in a substance that does not contain tobacco.

So I just want to make sure we're aware of that. If you have a novel product, and there are some out there, because our categories do not fit everything, we do have the Other category.

And the entire reason for having the Other category is to capture some of these products that are new and emerging that don't quite yet fit into some of the other, the cigar, the water pipe, the pipe, the ENDS, the cigarette, roll your own, and smokeless.

So we have actually had applications come in that utilize that. We are trying to take

record of that and see if we need to create a new category.

When submitting under the Other category, if you disagree with some of the categories FDA has, please provide your specification, but also please ensure we have that refuse to accept rule that you are providing all of the appropriate properties to identify the product.

All product categories for acceptance in an application are going to require that the manufacturer is identified, the product name is identified, the category, the subcategory, the package quantity, the package type, and the characterizing flavor.

If you don't have a characterizing flavor, we ask that you fill it out and state none. If you do have a characterizing flavor, we ask that you tell us what it is.

MR. CECIL: Great. Okay. This one has been identified as a question for Kim, but I think others have answers. You've got this.

Yes. She's here. She's hiding in the back. I see her.

If an EA is a standalone document, then why is an inadequate EA a reason for refusal to submit or a refuse to file? Particularly in other pathways, EX may generate an EA-based deficiency.

MS. STARK: Sure. So I'm going to actually attempt and I'm going to make sure that I'm looking at Dr. Benson that I get it right.

So the requirement for refusal to accept or refusal to file for the EAs actually stems from 21 CFR 25.15 and 21 CFR 25.40 and I kind of want to roll it out.

When CTP was added to the repertoire for FDA products, we actually went out with rulemaking regarding environmental assessments, categorical exclusions, and other types of environmental considerations, and with that we were added in to Part 25 that the rest of the agency is looking at.

When you look at the content for the

EA that is actually listed with the elements under 21 CFR 25.40. You then look earlier into the CFR for 25.15, and you're going to see that the agency actually could refuse to file if we didn't have an EA submitted in accordance with that, and we could also deny an application if we were missing certain elements associated with environmental considerations.

With respect to the SE program and the exemption request program, as we noted in earlier presentations today and yesterday, there is no filing stage. Because there is no filing stage, we are now looking at that under acceptance for 21 CFR 25.15. So that's kind of where the authority is coming from.

You guys can read it if you don't believe me, and I'm going to see, I think I'm missing something so she's going to come up here.

DR. BENSON: I think some of what's holding things up here is the use of the term an adequate EA. And if you look at the National Environmental Policy Act and then the FDA's

regulations, it's very limited. It's kind of high level, what it's telling you to look at. It doesn't get into the granularity to have a very thorough EA.

So to have an EA that's adequate for acceptance for filing really just has a handful of things that it says you have to have that in there. But for it to be an EA that could support a finding of no significant impact, you're going to need a lot more detail.

So that's where you might have an adequate one to get accepted and filed, but then down the road, before you're going to be able to market because you have not addressed the environmental aspect of our major action, we might have more questions for you.

Hopefully the ones that are on the website and those of you with experience doing this with SE, they'll be very thorough and there may not be any questions as we go along.

But I think the trip us is an adequate EA. That sounds like sufficient EA, and it's

really not. It's the bare bar that is in NEPA as well as the FDA's regs.

MR. CECIL: Don't move. Wait. There's another one. So this is another multi-part question.

So new uses of e-liquids is likely to be coming from a competitor product in the same category, so other flavors of e-liquids. So is this category a category-wide comparator? So in the majority of cases, a comparator will be product with a largely similar risk profile. Is that an acceptable comparator for these products?

DR. BENSON: So I'll go back to Dr. Rosenfeldt's talk where he said, what is the right comparator? It all depends, right? Is there a, this is the comparator you should use if you want an e-cigarette as a comparator? No. There isn't.

Usually what we would say is, again, you know, you're telling the story, so tell me why you use that comparator. Give me your scientific justification. It's because these are

the users of the product or these are the people we assume will move to using this product. Or this is a product that's very similar in its ingredients and its risk profile. Or this is a large market share, so we want to get some of that market share, so we think that's a great comparator.

So what is the correct comparator? Right now, there's a lot of factors in there, but it's on you to tell us the story of why this is the right comparator for you. And when I say the comparator, you could have several comparators in there. You're not limited to one.

MR. CECIL: And maybe one more. Yes, well, I'm pulling them all together since we've got you here. I'm taking advantage of it.

Could you tell us something about the expectations of the agency in terms of quality standards for the conduct of premarket population studies? Some are conducted based on market research standards, like other studies, like actual use, tried to apply the highest possible

standard, which often results in a mix of GCP, GEP, and ISO.

Same applies for data collection based on 21 CFR Part 11 compliance. Is that required? Data need to be submitted according to the CDISC. Thank you.

DR. BENSON: So --

MR. CECIL: If you insist.

DR. BENSON: The word population was in there, and I should identify, I'm the Director of the Division of Nonclinical Science, so humans and I don't really work together.

But I think at a high level, what that question is kind of about is, there are a lot of these guidances or best practices out there that govern studies that are usually done for the FDA, such as GLP, GCP, ICH, ISO, things like that, which by nature really, at least a lot of them, don't encompass the Center for Tobacco Products, at least not yet.

But does that mean they're useless to you? No. They aren't. So like GLP, I think

there's a draft out now that includes us, but it's not a requirement yet because we're not in a final rule there.

But would it benefit you to have any nonclinical study that you've done be done by GLP? It sure would. ICH, from a nonclinical standpoint, has lots of information on the proper way to conduct certain studies in toxicology.

Does that help you to follow that? Yes. It absolutely does. You might have to amend it a little, but saying it is primarily following ICH recommendations is hugely helpful to us. So I think although we're not absolutely in a lot of those regulations yet, are they helpful and can you follow them? Absolutely.

MR. CECIL: Iilun, do you want to add on?

DR. MURPHY: No, I echo Dr. Benson's thoughts. But basically, you know, if you follow standards that exist then it just strengthens the equality of the data that are produced.

And I would say that, you know, the

standards may be different for a focus group or a marketing survey versus a clinical study. And so for each type of study or analysis you're doing, I would encourage you to follow best practices.

Are there currently requirements for Center for Tobacco Products? No, but again, that doesn't mean that we don't encourage you to follow best practices.

MS. ALLARD: Can I add before you move on?

MR. CECIL: Yes, you can. I saw your name on that part, too.

MS. ALLARD: Yes. So unlike other centers, CTP doesn't have requirements for submitting clinical and nonclinical data in CDISC standards, which include SDTM and SEND for study data.

That doesn't mean that it's not helpful if you have data in that standard format and are able to submit it to us. It does enable us to do standard analyses using some of our data analysis tools.

And we do work pretty closely with our colleagues in other centers who use that data and we share tools. So if you're interested in submitting it, and you're concerned that it may be problematic, I would say consider doing it anyway and submit a question to our e-Submissions help desk and we can help you with test submissions, so that we can receive those types of data files, and they do benefit our data analysis when we receive them.

DR. BENSON: I can't say we have received things in the SEND format in my division, and I had a handful of folks get trained on it and now they haven't been using it, so please send more so more people can get trained on it and get used to using it.

It is really helpful because it generates things that otherwise we sit there and have to enter data and generate ourselves.

MR. CECIL: All right. Now, just for a little housekeeping, we're going to go for about 10 more minutes on the Q and A and then

we're going to start to bring this to a close. So those of you who are holding out and, you know, need a bio break at some point, we understand. We do have a few more minutes left, but I just want to give you a time check.

So all right. So we are conducting our CT and human factors using our six milligram per milliliter product at a 10 milliliter per day use, or a 60 milligrams per day. Does this level of use need to be on our labeling?

DR. MURPHY: So we don't have any requirements on the labeling. I think that if you have an intended use of your product and studies to support it, then we encourage you to describe that information and what we'll be doing when we receive it is we'll be looking to ensure that your labeling's not false or misleading and if we agree with the information that's there, then it would be authorized accordingly.

MR. CECIL: All right. FDA said that the comparative products should be legally marketed. As we understand that there are no

legally marketed ENDS products, can the applicant pick a comparator product without knowledge of even if the company is making a comparator product, will submit a PMTA?

DR. MURPHY: Do you mind repeating the question again?

MR. CECIL: I can try. The FDA stated that comparator products should be legally marketed. As we understand there are no legally marketed ENDS products, can the applicant pick a comparator product without knowledge of even if that company will be making a comparator product as a submission to PMTA?

DR. MURPHY: Okay. So we don't have any legally authorized ENDS products available at this time. However we know that consumers are able to purchase many ENDS products. So if you are planning to submit an ENDS PMTA and looking for comparators, sure, you know, use whatever available information is out there.

So I think that one could consider, you know, if you have a closed system, what are

the top most popular brands, whether it's the top five or top 10, and you can use that grouping as your comparator basis.

If it's an open system, again, what are the most popular products that are similar to yours that would be an appropriate comparator and what available information is there?

There are a lot of studies that have been done to date and will continue to accumulate more scientific information. And clearly they tend to, you know, study most popular products that are being used.

So I think that, you know, use what's available even if you don't have all the specific information because you're not the manufacturer. I think use the available information that you have at your disposal and bridge as best possible to the comparator products to let us know why you think that this is an appropriate comparator.

What information do you have to be able to compare based on broad categories. Even, like, what are the flavorings? What is PGBG?

What are the diluents? What is the nicotine concentration? You know, if it's open, or if it's an e-liquid, what are the devices that are typically used?

So there's a lot of considerations but you can try to specify as best you can but we understand that there are limitations.

MR. CECIL: Another comparator question. Again, I'll paraphrase this one. I'm making an e-liquid. What's my comparator product? Do I compare it to tobacco filler? And if that's the case, am I comparing the filler HPHCs to the e-liquid HPHCs? Or am I trying to find some other comparator product?

DR. BENSON: So I would go back to Dr. Rosenfeldt's slides where he showed that there could be an application for an ENDS product, so it could just be an e-liquid, that the right comparator there is a cigarette. Or it could be the right comparator is another e-liquid. So it would just depend on the application.

MR. CECIL: Okay. If I sold a RYO

tobacco on February 15th, 2007, and now sell a very similar product but market it as a pipe tobacco, will the FDA allow me to file and the FDA review an SE application as the two tobaccos, or only slightly different would be deemed to be from cross categories?

Yes, this one was, let me try. If I sold a RYO tobacco before 2007, and now sell a very similar product that's marketed as pipe tobacco, can I use the one that was sold in 2007 as a predicate for an SE?

MS. STARK: Okay so, I think this goes to reading of the proposed SE rule as well, where we talked about predicates within the same category or using predicates outside the category.

Currently we do not have any finalized rule implemented in place for the SE program. So as of today, an adequate predicate is going to be what you deem with the content in your application to support that, meaning you have a predicate that was grandfathered and you are

going to state what the differences in characteristics are between that grandfathered product or the one previously found SE and your new product.

If that means your grandfathered is RYO filler and your new one is pipe filler, currently without any type of rule in place, because I know what was proposed, we did limit the categories, that is applicable.

I do know that the comment period for the SE rule has closed. We're reviewing those. We're going to try to have content come out as soon as possible but as of today, there is no requirement regarding a predicate being in the same category. So that is applicable to do.

MR. CECIL: Okay. Can you change the name of a product that is subject of a PMTA order without submitting a supplemental application?

MS. STARK: A change in a name is not a new tobacco product. So therefore, you would not need to submit a supplemental PMTA for this. And it's not just for a PMTA. It's also if

you're changing the name for something that was authorized under the SE pathway or the exemption request pathway.

I will note there are other requirements that you need to be aware of as well. If you look under Section 905 for registration and product listing, we're looking for the listing of your products and your associated labels and advertisements associated with it, so you may need to make updates for that.

If you have post-market reporting under your PMTA and you're changing your name, that would be a nice thing to tell us as part of the post-market reporting. But I do want to note that just a change in name is not a new tobacco product.

MR. CECIL: Does the PMTA review process distinguish between products for inhalation versus products for oral application based on the obvious difference and potential risk? Does the PMTA review process differentiate

between?

DR. MURPHY: So we consider again the totality of the information and the route of exposure is a consideration. But we look at many different aspects. We look at, you know, the likelihood of initiation of a product, the use behavior, switching behavior, poly-tobacco use behavior, the toxicological risk profile, what we know about the health impact.

So I think that depending on what it is and the route of exposure, along with all the behavioral aspects, I mean, again, we consider many, many different parameters of the product and kind of overall make a determination that allowing the product to go to market would be appropriate for the protection of public health.

DR. BENSON: I can say toxicologically, obviously, route of administration matters, right? And so you could have a chemical, an ingredient in two different products that would be fine via one route from a toxicity standpoint, but via another route very

problematic.

Either, you know, transformation of something that you use orally in your liver that ends up making a toxic metabolite or something that you're inhaling and going directly at the lung and it has some lung toxicity or you're heating it and inhaling it and now you have brand new chemicals forming that wouldn't have formed if you were taking the product orally.

So obviously from our side in the tox world, that's a huge issue. So obviously we would look at those differently.

MR. CECIL: Okay. And again, this one I'm going to paraphrase slightly. Just received a last-minute text. And let me read to you what's here first, and then I want to modify.

So what products are required to submit a PMTA by May 2020? We've answered this a couple of times, but I think it's nice to be abundantly clear.

Does this include cigars and hookahs? I think if we were to be a little bit clearer

what needs to be submitted by May 2020? Not just PMTA, but also SE or EX.

MS. STARK: When you're looking at the compliance policy and the timelines with the recent ruling, we're looking at deemed tobacco product applications for new tobacco products. So I'm looking at cigars, pipes, water pipes, ENDS, Other, for those ones that fit in that Other bucket that may not fall under any of those.

So if you have a new tobacco product that is in the deemed category with a compliance policy, a product application will need to be submitted.

There are three options for applications, a PMTA, an SE report, or an exemption request. And I want to note, it's not submitted, it's receipt by CTP's Document Control Center, and there is a difference.

We have had things lost in the mail, and if they come in a month later, you may miss that date. This is why we're looking at our

portal, our electronic submissions. You don't have to worry about holidays. You don't have to worry about snowstorms or hurricanes, because our servers are open and can receive at horrible hours in the morning when most people are asleep.

So I'm going to encourage electronic submissions for all new product applications. If it is not a new product, meaning it was grandfathered, there is no requirement for an application to be submitted.

So that means if your deemed tobacco product was introduced or delivered for interstate commerce for commercial marketing in the United States, as of, meaning on February 15th, 2007, that is a grandfathered product that is not new, there is no requirement for an application to be submitted.

However, if you introduce your product in the U.S. after that date or you modify that product after that date, with our compliance policy, FDA should be receiving a product application by 11:59 p.m. on May 12th, 2020.

And I want to note it is our Document Control Center here in CTP. If it goes to a different Document Control Center and takes a few days to get over, it's when our CTP DCC receives it.

So again, look on our website for our address, our operating hours for physical mail delivery, and obviously use our portal for electronic submissions.

DR. CECIL: This is the rapid fire round. You have four questions left. All right. And I think we can answer these pretty quickly with perhaps one word on some of these.

So, how does OS intend to conduct its review process for the PMTA submitted by May 2020 given the court mandated one year for review and decision or requirement for removal of products from the market?

Does CTP intend to expedite review in any way? Yes. Okay next.

MS. STARK: We're prepared to receive and review and make timely decisions. What would

be, what would increase our efficiency is ensuring a complete application upon receipt.

MR. JONES: And also, if you're going to group submissions using something like a spreadsheet, like Crystal talked about, would really help us get access to that data more quickly.

MS. ALLARD: Yeah. And the more electronic information we receive, the better able to automate the process further down in the review process we are, right.

So, if we're looking for efficiency, paper, paper does not support that.

DR. CECIL: Next one is, unfortunately I know this one, who answers this one, when should we expect the 2017 amendments to the one side of t-test memo for the equivalence comparison of HBHC data to be published on the FDA website?

I did not know that it was not posted yet. But do we have a time-line for its posting?

MR. JONES: So, this question is

referring to a website where we've got several cites, policy memos posted, those, we referenced those I think during an earlier presentation.

We're going to continue to try to get more documents up on that website. I don't have a specific time frame, but just within the last few days we've put up, I think, a couple more cites, policy memos and some other documents which we call reviewer guides.

These documents were also written to assist the FDA reviewers with doing their reviews.

So the, you know, if you look at the website you'll see there's appropriate disclaimer language indicating that these documents represent our current thinking at a point in time.

I know earlier there was mention that some of those documents were written a few years ago.

Those memos certainly might change and get updated at some point at some point but

you're welcome to look at those and monitor that website for any future additions.

DR. CECIL: All right. And then there were two. The scientific review policy memos are very useful. Can FDA please post one for how SE reports should be tailored for premium cigars and their unique characteristics?

MR. JONES: So, I don't think we have that memo yet, but if we, if we develop such a memo for the FDA review staff then we would try to post it.

DR. CECIL: Last one. For ENDS products what is the requirement or recommendation to test the effect on nonusers of secondhand smoke exposure?

DR. BENSON: Obviously not any requirement for it and I really feel like that's one of the things that you don't necessarily have to specifically test for, right.

So, if you are characterizing the aerosol and you know the potential for exposure that way, you could address the nonuser exposure

to second and third hand aerosol through that.

I don't see that it's something that requires separate testing.

DR. CECIL: All right. With that, I'd like to say thank you to the panel. You help up well.

There are, we do have a couple more speakers to close the meeting out and I'll give you a chance to find your seats and we'll ask Brittani Cushman to come up and offer her closing remarks.

(Applause.)

MS. CUSHMAN: All right. Thanks everybody for your time yesterday and today. A big thank you to FDA, CTP and the personnel who are both here in the room and online for your time, for your preparation for this workshop.

Industry is extremely appreciative of these types of events because as one of my colleagues would say, FDA is a contact sport and what I mean by that is not football or flag football but the more contact we have, the more

both sides learn about the process.

We have seen significant progress in the flow of information with regard to both SE, PMTA and of course the SE exemption pathway, whether it be the proposed regulations, the final PMTA guidance, the scientific policy memos.

This workshop and I would also note other engagements that FDA personnel participate in, the industry basing-type workshops that are out there, we greatly appreciate your participation in those.

And we know you're not required to do that but we greatly appreciate the interactions there. All that being said, we, I would say, have some continuing issues that I'll just highlight a handful of those based on what we've talked about today.

Several people associated with FDA, maybe not those in the room, but continue to say, you know, why have manufacturers not completed these applications, why have they not been filed.

And I would say, you know, just like

you all were receiving this information incrementally and we want to make sure that we're submitting high quality, complete applications as best we can.

And for us that behooves us to get as much information we can for as long as we can prior to putting those applications in.

One example of that, that we learned about yesterday was some information that Crystal highlighted on some better ways of providing the formatting for applications.

And I think for many of us in the room perhaps that was the first we've seen of the modular approach and perhaps putting it in that format versus some of the methods and Tables of Contents we've seen previously.

And I know at least for my company and for others, we've been working forward on the previous way of looking at the Table of Contents versus this modular approach.

So, while that's not perhaps substantively changing our process for

application, it is a very time consuming way of reworking what we're putting together to try to put it in the best, most complete method for you all to review.

The other issue that I would highlight that came up in the past two days was this idea of minor versus major amendments and trying to delve into what that means and what the differentiating point is between those two.

And I'll talk about it a little bit more in a minute but in terms of just timing, you know, I look at it is it better for a company to get something on file that perhaps isn't entirely complete and then make some sort of unsolicited amendment later.

Would that amendment be considered minor or major and if a major solicited amendment were to be submitted later on, what does that do to our 12-month timeline if you have two 180-day periods that you're looking at back to back. Let alone if you add in any processing time in between.

So, the other issue, I actually heard some chuckles in the room, it may have been the only time I heard a lot of people laugh, which was, there was the suggestion that we should have a pre submission meeting 12 months in advance of our filing.

And considering the May 2020 deadline is not 12 months away and I don't have a time machine I certainly was one of the people in the room that laughed a little bit at that and I understand the spirit behind, which is, you know, you should get it as early as possible to have a pre submission meeting.

But I think it is a little bit of an acknowledgment of, you know, how difficult this process is that you would need to have a pre submission meeting at least a year in advance.

And I hope that gives some sympathy to those at the agency in terms of what those of us in the industry are going through to try to continuously be building the plane while we're flying it in terms of getting our applications

in.

So, you know, obviously I could give a number of examples and I think my industry colleagues did a great job of providing, you know, some questions and some things for the agency to think about on a number of these points and other points.

But I'd like to close out by looking at how to look at this going forward and particularly in light of some of the comments made in the Maryland lawsuit about, from the PMTA standpoint for ENDS, it's not a good idea to clear this market of a large number of the products that are out there from a public health standpoint.

And so, a few things that I took away from this was that perhaps unsolicited amendments are going to play a big part in the applications given the short runway we have before filing.

I believe that this would be in the interest of both FDA, who will want complete high quality applications and industry who want to

provide you with complete high quality applications and simply may not be able to do so in the time frame before us given that we're still learning about this process.

Companies may be able to file applications that are, you know, perceived to be in process with time-lines for completion of the various elements of the application and later supplemental filings or amendments or, you know, whatever nomenclature you'd like to use for that.

And I'd look at that as similar to how previous iterations of the extension requests were handled, which was to say we're working on this, this is the time-line we expect and this is the rationale for why we need this time-line.

And, you know, looking at the six months we have before us ahead to May 2020, I've talked to a number of the lab vendors and the consultants that work on these projects and I can tell you from the industry perspective, we're beginning to hear that they're just not accepting clients anymore.

And so, for those trying to continue to fill out their application, and I use the term fill out from the standpoint of, make them more complete, you know, we're running into the barriers of just finding places to get a lot of this work done.

Or we're finding that we're needing to supplement what the studies are and when we go to them they say well, you're going to the back of the line or we no longer have the ability to add that onto your study.

So, those are just a few things that we're running into and I would, you know, remind everyone that those who have products on the market today, we're facing the proposition that we may file something and if it's deemed to not be complete, we're having to pull those products from the market.

And we're not likely to be bankrolled to go back and try again. The fact of the matter is that from a manufacturer's standpoint our respective approaches may change again from how

they look today based upon the publication of the final guidance policy that we expect to be coming out with regard to flavored products.

And companies will have an even more difficult decision to make as to whether to continue to navigate this process or to simply give up due to the complexity cost or the shifting landscape before us.

I think in many cases that would be a shame both from the standpoint of the industry but also from the standpoint of offering lower risk alternatives to adult smokers and continuing to encourage industry to provide those alternatives.

Going forward enforcement will become of utmost importance. Good actors cannot function in a market where bad actors are allowed to proliferate in the absence of strong enforcement.

We as an industry continue to deeply and sincerely appreciate FDA's efforts to provide information and feedback and to improve these

processes and we hope that the flow of information can continue going forward.

Thank you all for your time, for your efforts and for the productive conservations the past two days and hope you enjoy the rest of your day.

DR. CECIL: Thank you very much, and for the final closing remarks, let me turn to Julia McGinn-Rodriguez.

MS. MCGINN-RODRIGUEZ: So, there are a few still left in the room, thanks for holding out. We really wanted to make this as meaningful and enriching an experience for you as possible.

So, I want to thank our colleagues from CTP for extending their time with us through later today and for really engaging with the audience.

As well as for those who served on the panel with us from industry and those who submitted questions to us in advance of the meeting in person and by phone.

It really allowed for us to have as

much information flow as possible and to Brittani's point to really help facilitate this contact sport. We were greatly looking forward to this opportunity to provide as much meaningful information to you as possible.

I would just like to quickly recap from the first day in the morning there are a number of resources that were provided and the Redus provided, the presentation provided by Ms. Redus.

You're going to want to look back at those links to just familiarize yourself with a number of different resources that we have on the website.

Ms. Allard, who spoke after that, presented later, had a lot of tips in terms of some of the digital resources that are available to you as well. Just a CliffNotes version of some of the suggestions she had if you want to take advantage of those.

You know, making use of eSubmitter, the Portal, testing your submissions early,

submitting your IAM requests at least a couple of weeks in advance because that can take a little bit of time.

And then check back in later also for updated, an updated version of the textback document because we anticipate that we'll be updated that and if you check frequently you'll be able to see newer iterations of that.

And she'd also mentioned that there's an RSS feed and I just want to plug that so you can actually sign up. It's a subscription basis on the different pages where you want to have an opportunity for automated updates to monitor any changes that are occurring on the website.

So I had actually asked for, I was just out of curiosity, how many questions we had received and actually answered in this short two-day session.

So, during the panels and advance of the senior leadership meeting, panel hearing we had 81 questions that we answered, which I find gratifying because it really gives us an

opportunity to address as much as of the input that we're receiving from the public as possible.

If you have outstanding questions, again you can reach out to your regulatory health project manager or the Call Center, CPT's Call Center, Office of Small Business, Office of the Ombudsman.

If you don't know where to go, you can address general questions to askctp@fda.hhs.gov.

So, in summary I'm not going to keep you any longer, thank you so much for your thoughtful engagement and great questions. This concludes our Fall public meeting.

(Whereupon, the above-entitled matter went off the record at 4:33 p.m.)

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C E R T I F I C A T E

This is to certify that the foregoing transcript

In the matter of: Deemed Tobacco Product Applications: Public Meeting

Before: US FDA

Date: 10-29-19

Place: Silver Spring, MD

was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

/Neal R. Gross/

Court Reporter