

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

2 8:33 a.m.

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

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

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

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

22 So, I get the chore of talking to you

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

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

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

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

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

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

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

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

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

5 If you're in the room, there are 3 by  
6 5 cards that are being handed out. If you need  
7 one, just raise your hand. Once you have filled  
8 out that card, because it's going to be such a  
9 full room we hope, hold your hand up a little  
10 higher so that the people can see that you have a  
11 finished question you'd like to hand up to the  
12 moderator.

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

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

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

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

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

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

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



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

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

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

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

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

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

11          So for example, overall population  
12          health risk would include information on  
13          population models, user behavior studies,  
14          epidemiology studies. And, for example,  
15          individual health risk evidence would include  
16          information on product manufacturing and  
17          distribution; information on toxicology studies,  
18          clinical studies, HPHCs and so forth.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Another scenario in which the identity

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

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

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



1 very low HPHC-level product.

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

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

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

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

1 considered in the overall APPH evaluation.

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

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

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

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

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

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

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

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

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

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

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

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

1 time or will it not?

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

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

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

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

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

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

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

22 So this is a very busy slide so I'm

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

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

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

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

1 one that is supposed to replace the new product.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

22 PMTA reviewers cannot consider results

1 generated with advertising containing modified  
2 risk claims.

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

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

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

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

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

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

22 So, example potential impacts of

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

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

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

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

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

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

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

22 Product use patterns are useful in

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

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

10 (Applause.)

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

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

22 All right. This is a large panel. We



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

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

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

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

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

1 product is appropriate for the protection of  
2 public health.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 DR. CECIL: Thank you. Elaine?

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

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

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

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

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

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

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



1 deadline.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And FDA is also proposing that abuse

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

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

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

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

3 DR. CECIL: Thank you, Elaine. Steve?

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

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

22 There is no doubt as to the paramount

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

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

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

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

1 they cite lack of clarity and direction from FDA  
2 on what needs to be included in the PMTA.

3 However, in my opinion with regard to consumer  
4 research, I think FDA has provided significant  
5 clarity.

6 A thorough review of publicly related  
7 documents, including information from the MRTP  
8 applications on General Snus, Camel Snus, IQOS,  
9 22nd Century and Copenhagen reveals significant  
10 insight into what FDA expects from consumer  
11 research in terms of study design, sampling, data  
12 analysis and reporting.

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

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

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

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

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

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

21 I feel confident that continued  
22 collaboration between industry and FDA will



1 result in sensible, justifiable and  
2 scientifically-robust research.

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

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

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

21 DR. CECIL: Thank you, Steve.

22 MS. TALBERT: Good morning. My name

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

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

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

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

1 clinical science and we have toxicologists and  
2 environmental scientists.

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

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

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

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

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

1 wanted to double-check.

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

5 DR. CECIL: And voluminous, yes.

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

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

15 (Off-microphone comments.)

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

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

22 DR. MURPHY: Right, I don't think

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 DR. CECIL: Right.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

12                  DR. CECIL: Certainly.

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

15                  DR. CECIL: Zero.

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

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

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

1 DR. CECIL: You may.

2 DR. ROUND: Okay. Pretty general.

3 Well I would say first of all, that is one area I  
4 think in the final guidance there is some  
5 discussion around, you know, bracketing high and  
6 low nicotine concentration products, except for  
7 the rest of the product is exactly the same.

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

11 (Off microphone comment.)

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

17 DR. CECIL: Is FDA behind that?

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

22 DR. MURPHY: So again, it really

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 reasonable approach in the context?

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

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

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

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

22 So, for example, if you're going to

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

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

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

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



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

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

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

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

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

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

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

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

17 For example, in the case of like a  
18 smokeless tobacco product. You know, if a  
19 manufacturer is comparing to let's say the top  
20 10, you know, market sellers, I think there is  
21 sufficient publicly available literature to  
22 generally say what the HPHC levels are generally

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

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

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

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

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

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

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

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

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

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

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

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

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

1 recommendations.

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

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

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

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

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

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

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

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

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

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

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

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



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

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

9                   DR. ROUND: Can I just add --

10                  DR. CECIL: Please do.

11                  DR. ROUND: -- perhaps, or maybe ask.

12 I assume that's the case for any PMTA for  
13 example, not just one, you know it's open-liquid  
14 specific or something like that. I mean it is  
15 our responsibility as the applicant to tell FDA  
16 why we believe -- why we've chosen the data or  
17 the studies that we've chosen and why we believe  
18 our products are appropriate for the protection  
19 of public health.

20                  DR. CECIL: You're absolutely right.

21 They can't hear me nodding. Anyone want to add  
22 on more to that? All right. Let's move on to

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

4 Does non-prescription drug products  
5 2010, guidance I presume, apply to ENDS and e-  
6 liquid labeling comprehension studies?

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

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

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

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

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

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

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

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

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

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

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

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

22           So, Dr. Rosenfeldt listed in his table

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

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

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

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

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

1 exposure that may impact use behavior and health  
2 impact.

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

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

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

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

1 depending on the route of administration and  
2 other factors.

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

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

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

1 perspective?

2 DR. ROSENFELDT: So both the TPFM and  
3 the PMTA will be reviewed. If there is an issue  
4 with the TPFM, my understanding is that the  
5 company will be -- the PMTA submitter will be  
6 notified. I believe that is what will be  
7 happening.

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

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



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

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

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

16 DR. CECIL: Right.

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

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

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

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

8 This individual asked, said we have  
9 400,000 SKUs and all e-liquids. How would you  
10 recommend that they trim down the number of  
11 applications they need to submit, or the number  
12 of the amount of testing that would be necessary  
13 to a point at which it is achievable from their  
14 perspective? Or from your perspective?

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

22 You know, in terms of what are the

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

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

13 DR. CECIL: It's a big number.

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

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

1 down.

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

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

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

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

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

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

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

7 (Whereupon, the above-entitled matter  
8 went off the record at 10:14 a.m. and resumed at  
9 10:37 a.m.)

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

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

1 our first speaker.

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

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

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

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

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

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

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

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

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

1 closed.

2 It is important to note that SE  
3 reports for deemed products will all be  
4 considered regular reports as their applications  
5 were not eligible for acceptance at the March 22,  
6 2011 deadline. These products include cigars,  
7 pipe tobacco, water pipe, ENDS, and other  
8 regulated tobacco products not included in the  
9 TPA.

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

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

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



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

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

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

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

18 Health Summary Health Statement. All  
19 SE reports must contain either a Health Summary  
20 or a Health Statement. This is not the same as  
21 submitting tobacco health documents under  
22 904(a)(4). A statement that you do not have

1 documents regarding health or behavioral effects  
2 is not acceptable.

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

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

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

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

1 your-own must also comply with product flavor  
2 standards.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 letter will be posted to FDA's website.

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

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

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

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

22 Phase 1 starts upon receipt of the



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

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

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

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

1 one of these letters, you will.

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

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

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

22 Our goal for these updates was to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Administration's Actions on Substantial  
2 Equivalent Reports.

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

10 Next, we will discuss SE metrics and  
11 program accomplishments. I will not be  
12 discussing the performance goals for Fiscal Year  
13 2019 or FY19 as we have open cohorts. We intend  
14 to post all performance goals in January 2020  
15 similar to past years. However, I do have other  
16 metrics which may interest you.

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

1 tobacco is included in roll-your-own metrics.

2 As a reminder, FY19 runs from October  
3 1, 2018 through September 30, 2019. As of  
4 September 30, we have received 229 applications,  
5 62 of which are open which means they are within  
6 FDA's review process, and 167 of which are  
7 closed.

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

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

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



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

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

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

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

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

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

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

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

13 (Applause.)

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

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

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

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

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

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

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

1 stand-alone GF determination request program.

2 Secondly, a GF review may occur under a  
3 substantial equivalence report or SE report for  
4 short, when a GF tobacco product is used as a  
5 predicate.

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

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

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

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

4 So let's first talk about what is a  
5 grandfather tobacco product? Well, a grandfather  
6 tobacco product is a tobacco product that was  
7 commercially marketed, other than exclusively in  
8 test markets, in the United States as of February  
9 15th, 2007. Just a reminder if -- and if you  
10 don't already know, FDA interprets the phrase as  
11 of February 15th, 2007 as on February 15th, 2007.  
12 And that's in guidance available on FDA's  
13 website.

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

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

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

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

8 So let's now talk about our reviews of  
9 voluntary stand-alone GF determination requests.

10 So an initial question may be who submits a GF  
11 determination request? Well, if you are a  
12 manufacturer and believe that your tobacco  
13 product should be considered a grandfather  
14 tobacco product and you'd like FDA to make a GF  
15 determination for your product, you may submit  
16 that request to FDA.

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

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

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

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

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

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

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

15 And if you have any questions about  
16 the voluntary GF you have submitted, you can send  
17 any questions you have to the email address  
18 above, [ctp-grandfather@fda.hhs.gov](mailto:ctp-grandfather@fda.hhs.gov).

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



1 submit an SE report, SE exemption or PMTA  
2 instead.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 have a flavor.

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

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

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

1 the United States as of February 15th, 2007.

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

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

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

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

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

5 Okay. So the third key component of  
6 your submission is evidence of commercial  
7 marketing in the United States as of February  
8 15th, 2007. On this slide I've listed some  
9 examples of documentation that you may include  
10 with your submission to help demonstrate the date  
11 of commercial marketing for your product.

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

18 If you're unable to provide  
19 documentation specifically on February 15th,  
20 2007, FDA suggests that you provide documentation  
21 of commercial marketing for a reasonable period  
22 of time before and after February 15th, 2007.

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

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

15          Again, if you're unable to provide  
16          documentation specifically on February 15th,  
17          2007, FDA suggests that you provide documentation  
18          of commercial marketing for a reasonable time  
19          period before and after the grandfather date.

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



1 an RFI for short, based on our experience.

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

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

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

1 one place but not in others.

2           Okay. So the second one up there, we  
3 see an evidence provided that does not  
4 demonstrate commercial marketing of the tobacco  
5 product in the United States on February 15th,  
6 2007. And third, we've seen situations where the  
7 collective evidence of commercial marketing, if  
8 we're in that scenario, in the United States  
9 before and after February 15th, 2007 is not  
10 adequate.

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

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

1 Agency puts forth in this regard.

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

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

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

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

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

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

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

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

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

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

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

22 Okay. So as I stated, a grandfathered

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

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

12 Substantial equivalence means, with  
13 respect to the new tobacco product being compared  
14 to the predicate tobacco product, that FDA has  
15 found that the new tobacco product has the same  
16 characteristics of the predicate tobacco product  
17 or has different characteristics and the product  
18 does not raise different questions of public  
19 health.

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

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

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

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

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

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

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

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

22           So secondly, if there's no reference



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

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

15 And then for questions regarding GFs,  
16 please use the email address listed there at the  
17 top there. The [ctp-grandfather@fda.hhs.gov](mailto:ctp-grandfather@fda.hhs.gov). And  
18 with that, this concludes my presentation. Thanks  
19 for your attention.

20 (Applause.)

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

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

4 (Whereupon, the above-entitled matter  
5 went off the record at 11:27 a.m. and resumed at  
6 12:32 p.m.)

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

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

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

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

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

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

14           (Laughter.)

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

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

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

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

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

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

1 and environmental science.

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

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

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

22           Generally in SE reports, we receive

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

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

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

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

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

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

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

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

1 nitrosamines like NNN and NNK.

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 There sometimes may be discrepancies

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

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

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

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

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

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

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

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

22 (Applause.)

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

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

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

22 FDA suggests that certain HPHC yields

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

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

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

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

22 FDA is currently seeking public



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

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

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

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

1 mass of tobacco.

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

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

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

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

1 change over a range of different smoking  
2 conditions.

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

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

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

1 N/A in your application.

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

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

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

1 smoking regimens that have been internationally  
2 developed.

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

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

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

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

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

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

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

1 the product undergoing testing.

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

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

17 Selectivity is the ability of an  
18 analytical method to differentiate and quantify  
19 the analyte of interest in the presence of other  
20 matrix components present in the sample.

21 Selectivity is generally established at the  
22 limitative quantitation.

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

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

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



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

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

11          (Applause.)

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

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

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

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

16 So let's begin with a brief discussion  
17 of FDA statutory and regulatory authority for  
18 this pathway. FDA statutory authority for review  
19 of exemption requests comes from Section  
20 905(j)(3)(A) of the FD&C Act. FDA's regulatory  
21 authority for exemption requests comes from  
22 first, the exemption rule under 21 CFR 1107.1

1 which became effective on August 4th, 2011.

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

7           Second, as presented earlier, the  
8 Refuse To Accept or RTA rule under 21 CFR  
9 1105.10, which became effective on January 30,  
10 2017, applies to all tobacco product application  
11 types. This rule established when FDA would  
12 refuse to accept a tobacco product submission or  
13 application because the application has not met a  
14 minimum threshold for acceptability.

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

22           First, the new tobacco product is

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

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

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

22 First, FDA reviews the exemption

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

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

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

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

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

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

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

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

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

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

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

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

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



1 by minors, toxicity, addictiveness or abuse  
2 liability.

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

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

14 For tobacco product identification, it  
15 is beneficial to FDA to include this information  
16 in a readily identifiable table or section of the  
17 application. Finally, resources are available on  
18 the FDA website on requirements and  
19 recommendations for the creation of an EA. These  
20 resources include webinars, recordings of the  
21 2018 public workshop and examples of EAs.

22 As we now have an understanding of the

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

7 If FDA issues an exempt order letter  
8 for the new tobacco product under Section  
9 905(j)(1)(A)(ii) of the FD&C Act, it requires  
10 that 90 days prior to the introduction or  
11 delivery for introduction of the modified tobacco  
12 product, the manufacturer shall submit a report,  
13 the abbreviated report, which will demonstrate  
14 the following.

15 That the product is in compliance with  
16 the Act. All modifications are covered by  
17 exemptions granted by FDA, meaning a found exempt  
18 order letter has been issued. The modifications  
19 are to a product that is commercially marketed  
20 and actions have been taken by the manufacturer  
21 to comply with the requirements under section  
22 907, if applicable.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10           The eligibility of the original  
11           tobacco product, the grandfather status,  
12           previously filed SC, statement identifying the  
13           commercial eligibility of the original tobacco  
14           products.

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

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

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

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

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

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

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

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

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

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

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

22 Finally, in applications requiring



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

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

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

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

22 If there are multiple increases,

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

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

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

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

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

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

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

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

22                   Additionally, did you provide the

1 amount of the additive contained with the glue?

2 Last, when looking at the example, the  
3 identification of supplier should provide, as  
4 well as the comparison of what is identical  
5 versus what is different between the additives.

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

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

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

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

22 For the second bullet, we are looking

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

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

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

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

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

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

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

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

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

1 filter to a non-filtered product.

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

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

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

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

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

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

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

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

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



1 products for both fiscal year 2019 and  
2 cumulatively.

3 This table provides metrics related to  
4 the exemption request pathway for statutorily  
5 regulated products for fiscal year 2019. As a  
6 reminder, fiscal year 2019 runs from October 1st,  
7 2018 to September 30th, 2019.

8 So therefore as of September 30th,  
9 2019, we have received 347 exemption requests, 85  
10 of which are open within the FDA review process  
11 and 262 have closed.

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

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

22 This table provides the recent metrics

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

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

8 So, this concludes the presentation on  
9 the requests for exemption from substantial  
10 equivalence pathway or exemption requests.

11 Dr. Walters and I would like to thank you for  
12 your attention during our presentation.

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

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

1                   (Whereupon, the above-entitled matter  
2 went off the record at 1:24 p.m. and resumed at  
3 1:25 p.m.)

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

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

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

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

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

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

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

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

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

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

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

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

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

22           The agency has acknowledged the role

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

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

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

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

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

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

14          Specifically, meaningful definitions  
15          of and metrics for determining same  
16          characteristic, different characteristic, and  
17          different questions of public health are  
18          imperative.

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

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

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

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

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

22 I'd like to briefly share some



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

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

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

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

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

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

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

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

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

1 study set.

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

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

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

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

1 directly influence the observed abilities in  
2 smoke HPHC deliveries.

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

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

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

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

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

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

10 DR. CECIL: You're free to comment.

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

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

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

1 clear for everyone.

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

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

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

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

20           Nomenclature, labeling correctly,  
21 using table of contents, making sure that it's  
22 clear information that it's clear what the

1 information is for.

2 That it's well annotated, that your  
3 links are working correctly. Even with the SE  
4 program being really mature, we're still having a  
5 lot of issues around understanding why you  
6 submitted something or is a table superseding  
7 another table, duplication of data.

8 All these very small things  
9 collectively can cause the process to be very  
10 inefficient. And as the office is preparing to  
11 maybe receive a large volume of applications, we  
12 are evaluating all of those programs. We are  
13 evaluating all of our procedures and processes.

14 People that know me well in the office  
15 with tell you I'm the queen of process  
16 improvement. And I can only do that if people  
17 understand sort of what the pin points are. And  
18 I encourage all of you to really think about when  
19 you're preparing your submissions.

20 It may seem logical to you to organize  
21 it in a certain way, but I encourage you to think  
22 about Ms. Allard's presentation and making sure

1 that information is clear, concise, direct, well  
2 summarized.

3 Some things for instance that we see in  
4 terms of a acceptance and if we consider us  
5 receiving, you know, hundreds of thousands of  
6 application, Lauren DeBerry previously presented  
7 and talked about you know we'll try to get  
8 everyone through the acceptance phase. Right?

9 Well, it seems like a low hanger. We  
10 have some basic regulatory requirements to make  
11 it through the acceptance phase. And yet, we're  
12 still seeing, I'm getting caught up and trying to  
13 understand whether you met those basic  
14 requirements or not.

15 And if applications were better  
16 organized, we could quickly get through those  
17 applications. Get you through phase one so that  
18 then we can spend more time thinking about how to  
19 group these, these applications so that they  
20 could be ready for scientific review, which is  
21 where you want to be.

22 So, creating inefficiencies just like



1 on your end. We're definitely doing the best  
2 that we can. Our project managers, some of whom  
3 presented today, are also leading a lot of work  
4 groups thinking about, rethinking how we process  
5 our submissions and what we could be doing  
6 better.

7 So, if you have any feedback, whether  
8 it's either through questions for us or -- you  
9 can send them to your project manager as an  
10 end-user and it's someone who's communicating  
11 with us. I encourage you to please provide that  
12 feedback because it will help us in the future.

13 Let me see if I got everything. And  
14 the appendices, I think at the beginning of the  
15 panel you mentioned the appendices are provided  
16 in the acknowledgment letter and it might be a  
17 little too late because you've already assembled  
18 your application.

19 So waiting for your act letter may not  
20 be the best approach to putting together your  
21 application. So, I encourage you to monitor our  
22 website and to look at those appendices that are

1 posted on our website.

2 They're by product category and they  
3 will give you a better flavor of what the  
4 Agency's looking for and how to better organize  
5 your submission. And I'm done.

6 MS. STERNBERG: Hi, I'm Lori  
7 Sternberg. I'm Senior Regulatory Counsel in the  
8 Office of Compliance and Enforcement. And I am  
9 here not so much to convey information as to  
10 answer your questions.

11 In particular, my colleague Bryan gave  
12 us some information about the grandfather  
13 process, whether that be stand alone or as part  
14 of your SE application. And I'm looking forward  
15 to hearing your questions and concerns about  
16 that.

17 DR. CECIL: Thank you, very much. All  
18 right and we do have a number of questions. I  
19 spent some time trying to clump them all together  
20 into similar topics and there is not a replicate  
21 among them. So, there's lots of good questions  
22 here.

1                   So, I'll start with the -- can CTP  
2 please explain when and how CTP determines if  
3 only one round of efficiency letters is  
4 appropriate versus two rounds of deficiency  
5 letters?

6                   Some letters have the statement, we  
7 expect that no more deficiency letters will be  
8 issued for this application even if the letter  
9 was a first-round letter.

10                   Some letters have the statement, we  
11 expect that no more deficiency letters will be  
12 issued for this application even if the letter  
13 was a first-round letter.

14                   MS. BELTRE: Obviously, it's  
15 case-by-case. So, if the reviewers felt like  
16 they -- still? Sorry. Thank you. It's a  
17 case-by-case basis.

18                   If the reviewers, when they conducted  
19 their first round of scientific review felt like  
20 they had enough information and that maybe the  
21 deficiencies that were provided were enough for  
22 them come to a determination that, that

1 information may be included.

2 It's not drastically different from  
3 the previous process where we have the PFind  
4 letter. And then, what we call an AI letter.  
5 The difference is now, like Laura mentioned,  
6 they're combined.

7 And if the technical Project Lead felt  
8 that we have substantial information in that  
9 first round of the review and maybe they're just  
10 a couple of more deficiencies that need to be  
11 resolved, they may include that information in  
12 the first deficiency letter that goes out to  
13 communicate that.

14 That doesn't mean that, you know,  
15 that's the end of it. It could -- did I cover  
16 that correctly? You guys would you like to add  
17 anything? No? Okay.

18 DR. CECIL: All right. Please, feel  
19 free to jump right in.

20 DR. JUNKER: I mean, I would, I would  
21 just to whoever said that, I would recommend that  
22 you reach out to your RHPM. Because, I mean,

1 they're -- it never hurts to confirm that, that  
2 is actually a preliminary finding and it's not  
3 something that fell through the cracks and should  
4 been an AI.

5 MS. BELTRE: Yes. I would add to that  
6 the RHPM's not serving just as the liaison to you  
7 they are also a liaison to the scientific review  
8 team. Right? So, they're in a very special  
9 place in my heart and in the review process. In  
10 that they do get to see sort of both sides.

11 And you know, if it was an error or if  
12 you know, whatever, the case may be, they're in a  
13 better position to maybe reach out to those  
14 reviewers and asked for a clarification and may  
15 be able to convey better where you are in the  
16 scientific review process.

17 DR. CECIL: Great. Thank you, very  
18 much. All right. Next question. Are the  
19 manufacturing requirements and inspections the  
20 same for PMTA and SE? Also, are the requirements  
21 for an environmental assessment the same for PMTA  
22 and SE?

1                   Sure. Are the manufacturing  
2 requirements and inspections the same for PTMA  
3 and SE?

4                   MS. STERNBERG: I'm not sure I'm clear  
5 on the question. But manufacturing requirements  
6 the same? Or inspections the same? Which did  
7 you say?

8                   DR. CECIL: I, well perhaps if you  
9 could answer, are the manufacturing inspections  
10 the same? And as far manufacturing requirements  
11 go, I think, that is something the panel could to  
12 talk about separately.

13                   MS. STERNBERG: Okay. Our  
14 inspections, application-based inspections are  
15 designed to verify the information contained in  
16 the application. So, no matter what the  
17 application is, we are looking to --

18                   When we arrived on-site be able to  
19 verify the information you provided the agency,  
20 regardless of the pathway your application is  
21 going to take.

22                   MS. BELTRE: I guess, I would, I would

1 clarify that in terms, for instance, where the SE  
2 and the exemption program, inspections are not  
3 necessarily a part of the review process.

4 But they definitely can happen by  
5 annual leave, which is, you know, some of the  
6 activities that the Office of Compliance and  
7 Enforcement. So, if there's some confusion  
8 there --

9 MS. STERNBERG: Right. That's part of  
10 why I was -- well a little difficult to answer  
11 the question. We don't routinely do an  
12 inspection for an SE application. But a  
13 manufacturer that has a product, that is marketed  
14 is open to its biennial inspection.

15 Any manufacturers that is registered  
16 and listing products is subject to the biennial  
17 inspection. Any application that is filed is  
18 then subject to verification on inspection.  
19 Those are two different types of inspection.

20 DR. ROGERS: Okay. And then, with  
21 regard to the EA, there should be no difference  
22 in the different pathways and that -- right, yes.

1 DR. CECIL: All right. And another  
2 question for OCE. What is the time line for  
3 voluntary grandfather review? I think that would  
4 be --

5 MS. STERNBERG: So, there's no  
6 statutory deadline for the, there's no -- the  
7 grandfather application process is voluntary and  
8 there's no statutory deadline for the review.

9 DR. CECIL: Thank you.

10 MS. BELTRE: However, I would like to  
11 put a plug that having your GF stand alone before  
12 you submit your application for a seat is really  
13 helpful. Having EORG after determination in  
14 advance of an SE application, it's really  
15 helpful.

16 MS. STERNBERG: It's a two part  
17 analysis. So, you can file for a stand-alone GF,  
18 in which case, the Agency will make a  
19 determination about whether it's able or not able  
20 to provide you with grandfather status or as part  
21 of your SE application, you can point to a  
22 predicate and ask for a grandfather determination



1 about that predicate. If you're going to do the  
2 later, then you just have to go through the first  
3 period of time to make that GF determination.

4 And then, the period of time to  
5 determine whether or not it's at SE. So, they  
6 each will take the time they will take. Whether  
7 it's Stand Alone for GF and then Stand Alone for  
8 SE. Or as part of a combined package. Does that  
9 make sense?

10 DR. CECIL: All right. Ms. DeBerry  
11 said that an applicant had to request FDA to  
12 begin review of a response for deficiency letter  
13 if submitted in less than a 180 days. This is  
14 new information. Could you expound?

15 MS. BELTRE: So, with revamping our  
16 letters, we wanted to make sure that  
17 communication was clear. And that any  
18 assumptions that were being made were clearly  
19 articulated in the letter.

20 So, the new language that Ms. DeBerry  
21 pointed out states that each cycle is 180 days  
22 and until that time lapses, at day 181 we will

1 initiate review. What we see is applicants  
2 submit partial amendments.

3 They may submit an amendment that  
4 responds to, let say, five deficiencies. They  
5 have five deficiencies, they respond to five.  
6 Because the time frame to respond is --

7 It's significantly longer. It may  
8 mean that additional testing was done. And we're  
9 still within the 180 day clock and they may want  
10 to amend and provide additional information.

11 So, to avoid sort of that piecemeal  
12 approach, we will wait the full time the  
13 applicant has to amend their application to  
14 ensure that we have a complete response. And we  
15 would kickoff review at day 181.

16 If an applicant feels very confident  
17 that they've responded to all the deficiencies in  
18 all of the requests and would like us to initiate  
19 review before our established time line, they  
20 need to adjust very clearly articulate that.

21 We are not going to assume that  
22 because there are four deficiencies and you

1       responded to four that therefore this is a  
2       complete response. So, it was just a way to just  
3       be clear about the expectations after deficiency  
4       letters are issued. And clearly, there's an  
5       Amber Alert.

6                   DR. CECIL: Yes, another Amber Alert.

7                   MS. BELTRE: Hopefully, they find what  
8       they're looking for.

9                   DR. CECIL: I think, so. All right.  
10       Let me give one to Matt because we like to keep  
11       him on his toes. In the presentation on  
12       exemption pathways, removal of a complex  
13       ingredient was listed as a modification that may  
14       be considered minor. What about the addition of  
15       a complex ingredient or flavor?

16                   CDR WALTERS: So, I think that would  
17       be a review issue that we'll have to evaluate in  
18       a submission. I mean, if it ends up beyond  
19       chemistry, we'll have to evaluate then. I think  
20       it's more of a review issue. Then -- do you need  
21       me to answer that right here?

22                   DR. CECIL: I had another, I think

1 relatively straightforward. Of course, every  
2 time I say that they come out being very  
3 difficult. So, maybe this one will be too. Would  
4 adding a tobacco additive to a product that  
5 changes the characterizing flavor --- is it  
6 acceptable through the exemption pathway?

7 CDR WALTERS: Yes. I mean, I think  
8 it's a review issue. We'd have to evaluate that  
9 submission. I mean, in the examples that I  
10 provided of the cigar. I had cherry-to-cherry.  
11 And that was specific that it needs, it should be  
12 the same characterizing flavor.

13 DR. CECIL: There are a number of  
14 memos that have been posted on FDA's website.  
15 For the FDA, for all your own, the memo says that  
16 the quantity changes are no longer different  
17 questions of Public Health.

18 So, do we need to have a lengthy  
19 quantity change right up? Or can we cite the  
20 memo? It looks like, that it is unnecessary to  
21 work for the submitter and for the FDA reviewer.

22 DR. ROGERS: It is true that we have

1 a memo now, that lays out our current thinking  
2 about package quantity changes and the review  
3 process for FDA is fairly streamlined.

4 I think if the applicant decides to  
5 cite the memo and can explain why they feel that,  
6 that's adequate that they can do that.

7 DR. CECIL: Okay. Great. I'm trying  
8 to look, and I actually take one from online. In  
9 the panel discussion on PMTA review process  
10 yesterday, Christi Stark appeared to state that  
11 FDA would consider a new tobacco product  
12 authorized under a PMTA to be an acceptable  
13 predicate under the SE exemption pathway. Is our  
14 understanding accurate?

15 MS. BELTRE: Yes.

16 DR. CECIL: All right. For deemed  
17 products like pipes, there are no guidances  
18 available, yet. But I think I heard that the  
19 2020 deadline is also applicable for these  
20 products.

21 How are we going to do the  
22 submissions? Is FDA planning to provide some

1 initial guidelines? That would be talking about  
2 future plans and whether or not we're not going  
3 to answer that question. But, how are we going  
4 to review these submissions?

5 DR. ROGERS: Well, the one comment I  
6 would make is that we did post on our website the  
7 appendices that we keep referring back to that  
8 are part of the acknowledgment letters.

9 So, those are a good thing to look at  
10 to give you a sense of the types of information  
11 that we're looking for the new products. As to  
12 how we're going to evaluate them, I can't really  
13 speak to that right now.

14 DR. CECIL: This one has to do with  
15 PMTA, but it will still apply. Would it an  
16 e-liquid manufacturer be expected to provide an  
17 analysis of the vapor and or aerosol output given  
18 the variety of device options and settings?

19 CDR WALTERS: So, knowing that there's  
20 a diversity of devices out there. And so, I  
21 think, if you justify the wires, so I think ace  
22 are in device to measure HPHCs in aerosol and in

1 an e-way grid.

2 That would be one way to justify why  
3 you choosing this device and how it represents  
4 exposure to this particular chemicals.

5 MS. BELTRE: I just wanted to make, I  
6 just wanted to make a clarifying point. We did  
7 talk about resources that we currently have  
8 online. For instance, the appendices we tried  
9 our best possible with the limited information  
10 that we have. Right?

11 At this time to put out some helpful  
12 information that may help people sort of think  
13 about information to contain in their  
14 applications. However, the list of memos, the  
15 last time I look at it, it was quite extensive  
16 and long.

17 So, in addition to having, encouraging  
18 people to read through them, I also encourage  
19 people to look at when these memos were written.  
20 They are written in one point in time, in a  
21 specific context.

22 And as we learn more about these

1 products. And as we receive more applications  
2 and gain more experience, that would sort of  
3 evolve.

4 So, yes, it's useful information. And  
5 yes, people should be referring to them, but  
6 definitely just be cognizant of, you know, how  
7 the limited use they could have moving forward.

8 DR. CECIL: And also, I just want to  
9 jump in a little bit on question about the  
10 e-liquid manufacturers. Keep in mind that there  
11 are a lot of different devices out there. And  
12 the ingredients that you put into your e-liquid  
13 when heated to an elevated temperature will  
14 degrade.

15 And your understanding of the  
16 degradation and the effects of those degradation  
17 products upon a user is going to be an important  
18 piece of information in your applications.

19 At this point, no, I'm not. Talking  
20 about -- sorry. To repeat the question, are, are  
21 we talking about a standardized device?

22 I do not believe that there is a final



1 standard device to work from. I'm speaking only  
2 of the temperatures that have been reported in  
3 the literature for the coil temperature that can  
4 go 400, 500, 600 degrees.

5 At some point, you do need to  
6 understand what the degradation pathways are for  
7 the components that you put into your e-liquids.  
8 All right. That one is a question for me. So,  
9 I'll put that one off.

10 If a statutorily regulated product was  
11 under scientific review, an AI request response  
12 submitted, or deficiency request, when CTP  
13 changed the deficiency letter will a PF letter be  
14 issued for that product?

15 MS. BELTRE: The new deficiency letter  
16 covers the language that -- so, let me step back.  
17 In the PFind letter, the original PFind letter  
18 and deficiency letter had two things that were  
19 different.

20 One, the time to respond. And two, it  
21 had some boilerplate language about this may be  
22 your last chance before we move forward to a

1 final action. That language has been carried  
2 over to the deficiency letter and where  
3 applicable it will be inserted in your letter.

4 So, if the question was, that in terms  
5 of the difference or you're still sort of going  
6 to get the warning, this may be your last chance  
7 even if it's a deficiency letter.

8 And because there's no longer a  
9 difference in time line that becomes mute across  
10 the two different letters. So, no more PFind. I  
11 hope you all received a nice, fun, clean letter.  
12 And that you love it. And if you don't, that you  
13 tell us so that we can fix it.

14 DR. CECIL: Okay this is a long  
15 question, but I think it's quite a good one.  
16 Four, roll your own paper. Traditionally, we  
17 have HPHC testing performed on cigarettes that  
18 are made using the paper. We prevent access  
19 variability by putting tight limits on the RYO  
20 cigarettes.

21 For example, same type of tobacco. A  
22 certain amount of tobacco used, selected by a

1 pressure drop. Can also, only smoke by the CI  
2 method since they are wrapped weird. Have been  
3 asking the laboratory to double wrap the mouth  
4 end so that we have low variability.

5 But the manufacturer RYO, is very  
6 artificial. How do we connect the analytical  
7 data from this very artificial cigarette to  
8 questions of public health. And can we see  
9 analytical differences in our artificial  
10 cigarettes that are not, do not occur for  
11 smokers?

12 CDR WALTERS: So, make sure I  
13 understand. This is talking about how they would  
14 go smoking and roll your own tobacco, filler with  
15 fill-your-own paper?

16 DR. CECIL: Yes. This is for a -- I  
17 will interpret. So, for this, it's for a paper  
18 manufacturer, supposedly paper manufacturer. Is  
19 making test cigarette using a very consistent  
20 process by which to develop those cigarettes and  
21 smoking them.

22 But don't, do not necessarily

1 represent what the user might make. Is it still  
2 an important piece of information for FDA and  
3 even though they do not represent a market,  
4 likely outcome. And how are we going to evaluate  
5 those chemical differences?

6 CDR WALTERS: Yes. So, any smoking  
7 regiment is not a true representation of a  
8 consumer using that for a product. I do remember  
9 in our appendix we actually provide some  
10 suggestions.

11 In terms of how you may go about  
12 measuring certain HPHCs in the roll-your-own  
13 paper for select tobacco product filler, making  
14 sure that's consistent between a new and  
15 predicate product.

16 Between the two rolling papers, so  
17 that would be one. So, I would encourage you to  
18 look at the appendix because I know we weigh  
19 those for our companies.

20 DR. CECIL: And the follow up is  
21 actually a couple of questions, here, but we can  
22 combine them into one. Are cigarette paper

1 considered additives from the EX pathways  
2 perspective?

3 CDR WALTERS: Cigarette paper, yes,  
4 yes.

5 DR. CECIL: All right. That was two  
6 of those. That one we've covered. All right.  
7 This one might be for me too, so. If an e-liquid  
8 manufacturer uses only USP nicotine, does the  
9 manufacturer need to include a supplier of the  
10 nicotine?

11 If yes, does the application need to  
12 include samples made from both suppliers of  
13 nicotine USB? The same goes for PG and BG.  
14 Tagged.

15 The one thing I would say is that USP  
16 grade is a minimum standard. It does not say  
17 that this is, that they are identical. It just  
18 says you need me to be at least this good to be,  
19 consider your product USP.

20 And so, if you are changing your  
21 manufacturer, you would deal with it as if you  
22 are using any other manufacturer in a SU review.

1 If you are two different nicotines, we would need  
2 to look at those as different products or  
3 different components. Same with PG and BG.

4 I don't know yet. Let me come back to  
5 that one. Did I come close? Okay. I wanted to  
6 make sure. I'm trying to get some, one to get  
7 the panel, full panel involved rather than  
8 leaving this, you know, here. I've got one that  
9 can be messy. All right.

10 It appears to most of the industry  
11 including testing laboratories believe that  
12 requiring three batches and seven replicates for  
13 HPHC testing seems to be overkill. What would  
14 the industry say would be an appropriate number  
15 of batches considering the variability of the  
16 products? Okay.

17 DR. JUNKER: I appreciate that. I  
18 mean, I'll -- I really think it depends on how  
19 much variability you have in your product and  
20 your process.

21 What I would say is, is kind of what  
22 I said in my intro. I think the things that you

1 do to control for those factors can minimize the  
2 sample sizes you need.

3 So, if you're, you know, manufacturing  
4 these products on the same day, testing in the  
5 same lab, same equipment you know, for products  
6 that contain tobacco leaf.

7 If you're using similar or the same  
8 blend components pulled from similar sources of  
9 those tobaccos. So, so things -- there are  
10 things you can do to, that I think you can do, to  
11 minimize the sample sizes that you need.

12 MR. LONG: And I agree with Chris on  
13 that. And I would also say that, as we heard  
14 earlier today, is if the product is variable then  
15 the simple solution is just do more replicates.

16 I think the issue for the premium side  
17 of cigars would be that the product is inherently  
18 variable. And handmade nature of the product is  
19 essentially a characteristic of the product. So,  
20 I'm not quite sure where to go with this one.

21 DR. CECIL: Which is a fair question  
22 again taking at that next step. An inherently

1 variable product also has a variable level of  
2 risk associated with it.

3 And if you can help us identify a way  
4 to deal with that risk. Because if your one  
5 cigar is extremely high in HPHC and one's very  
6 low, there's a large variability certainly.

7 But we need to understand what the  
8 risk is to that end user to be able to determine  
9 whether or not these are substantially equivalent  
10 over, when comparing two of this, modified  
11 products.

12 MR. LONG: I would say again that  
13 right now where we are in this, the way it looks  
14 is, there's, there's so much overlap between the  
15 products that it's hard to really distinguish a  
16 difference between them.

17 So, you could almost argue that, you  
18 know, a cigar is kind of a cigar. Now, if you're  
19 talking about extremely small cigars to extremely  
20 large ones in smoke and light, you could argue  
21 that there are actual differences.

22 But in this middle ground of the



1 products that are primarily, that predominate the  
2 premium cigar market, they are almost  
3 indistinguishable based upon the results we're  
4 getting at this point.

5 DR. CECIL: All right. I will change  
6 the topic. I think there's more discussion  
7 certainly happening in the next section. I  
8 already queued one for the next section, so.

9 In the HPHC presentation, FDA  
10 indicated that non-intense and intense puffing  
11 regimens have been established for ends. FDA  
12 referenced an ISO method for the non-intense  
13 regimen.

14 Is that the same as the CORESTA  
15 recommended method? And what intense regime does  
16 FDA expect applicants to use for HPHC analysis of  
17 ends?

18 CDR WALTERS: So, the ISO method that  
19 was presented in based on the CORESTA method for  
20 ends. There is currently not any recognized  
21 methods, internationally-recognized methods for  
22 intense method for ends.

1           So, it would be suggested that if, to  
2 provide or document what intense regiment you are  
3 going to provide in your submission.

4           DR. CECIL: And keep in mind that the  
5 PMC, PMTA for ENDS guidance indicates that two  
6 different -- an intense and a non-intense testing  
7 protocol should be used. And that testing  
8 protocol does not simply mean puff protocol.

9           It also means temperature,  
10 potentially. It could mean different lengths of  
11 puffs. It could it end up being the number,  
12 changes in the variance or in your air flow  
13 through your ENDS device.

14           There a lot of different variables  
15 with an ENDS product that need to be defined.  
16 And you may use alternative approaches to dealing  
17 with an intense regiment, then simply changing  
18 the puffing protocol, like you do with a  
19 cigarette. And again, it would be up to you  
20 define what it is and what is appropriate.

21           All right we are almost at -- we've  
22 five more minutes left. So, for those on the

1 panel your time is almost done. Let me go back  
2 to our -- what exactly is required for an  
3 abbreviated report for exempt products? Is there  
4 a template or outline you all could provide?

5 MS. BELTRE: You will get an example  
6 in your exempt order letter. Is that --

7 DR. CECIL: Okay. That, that -- I

8 MS. BELTRE: What?

9 DR. CECIL: I was moving on to the  
10 next one. I'm sorry.

11 MS. BELTRE: Oh, okay. I didn't know  
12 if there was more to that.

13 DR. CECIL: If anybody is still  
14 confused, you can ask questions, ask CTP and  
15 we'll see what we can do there. Let's see, the  
16 AI and PF or PFind, deficiency letter, and there  
17 was a question as to what Ai and PFind are.

18 And so, I think they did want a  
19 clarification of what these things are and how  
20 they were used. Now, they've been replaced by a  
21 deficiency letter.

22 MS. BELTRE: Originally, we had a

1 advice/information request letter. We, I think  
2 in our last public meeting was our first sort of  
3 reiteration of clarifying the language and making  
4 it more plain, plain English and easier to  
5 understand.

6 It was sort of the first version of  
7 that process improvement. And as we evaluated  
8 all the letters, we started looking at making  
9 sure that things were labeled in a manner that  
10 they describe what was expected to be found.

11 Because advice/information, either  
12 your advising me of something, or you're  
13 requesting information, or are you doing both?  
14 And sometimes people would be confused by the  
15 title of the letter.

16 Sometimes, it would include requested  
17 information in those letters. Yet, when we talk  
18 publicly, we talk about deficiencies, and we talk  
19 about scientific deficiencies, administrative  
20 deficiencies. So, therefore we decided to change  
21 the name of the letter.

22 Acknowledgment letter is another one.

1 We're acknowledging receipt, but really were  
2 conducting a review to ensure that you meet  
3 regulatory requirements. And we're making a  
4 decision to accept your application.

5 So, that was another way that we felt  
6 like adjusting the language more articulated what  
7 the status of your application was versus the  
8 previous names of the letter didn't.

9 DR. CECIL: Let's see, as we have one  
10 more question, find a good one. Okay, Colleen,  
11 I'm sorry. What information specifically are you  
12 most interested in for stability studies for  
13 e-liquids.

14 The focus for smokeless was arguably  
15 microbial content. However, it could be argued  
16 through challenge studies that microbes cannot  
17 grow any liquids.

18 DR. ROGERS: Yes, so for e-liquids  
19 some of the things that we would be interested in  
20 would be PH, water activity. We would still be  
21 interested in looking at microbial content. I  
22 think challenge studies while they could be

1 submitted and could be used.

2 For challenge studies you would have  
3 to pick particular organisms for those. And if  
4 you were to do so, then you would have to explain  
5 why you picked the particular organisms that you  
6 did.

7 And then, depending on microbial  
8 content if any kind of microbial content was  
9 found, we might be interested in looking at  
10 endotoxin levels or aflatoxin levels to see if  
11 there's any of that present.

12 DR. CECIL: And I'll take up the one  
13 final question that was asked, had to do with  
14 analytical variability. There's actually several  
15 of them that speak to analytical variability.

16 And I think that we talked about it in  
17 the discussion of validation. And I think that  
18 the analytical methodology need to be clear to  
19 define.

20 When we're talking about variability,  
21 where is variability coming from? Is it coming  
22 from the analytical methodology? If it's a GC

1 mass spec, it's not likely coming from the GC  
2 mass spec.

3 It may be coming from the sampling  
4 process by which you either smoke your product or  
5 you aerosolize your ENDS product and collect it.  
6 And it is important to look at that level of  
7 variability.

8 And finally, it may be coming from  
9 your product. And if it is a product, it's  
10 important to identify that the product has  
11 variability that we need to understand and deal  
12 with. And I think that sort of information --

13 Inherently variable products are not  
14 necessarily the, a problem. We need to  
15 understand what it is. And understand what the  
16 effects of variable products are upon an SE  
17 application.

18 And that's -- we'll stop there. And  
19 say, thank you all. And before we release you  
20 all, I wanted to say, ask the audience to thank  
21 those who have spoken over the last two days.

22 And all of the panelists that have met

1 over the last couple of days for the all their  
2 time and concern. Thank you, so much.

3 We're going to take a 15-minute break  
4 and we will start off with the ask CTP  
5 leadership.

6 (Whereupon, the above-entitled matter  
7 went off the record at 2:16 p.m. and resumed at  
8 2:41 p.m.)

9 MR. CECIL: Sorry for the delay. We  
10 have a few individuals that need to leave early  
11 due to issues of one type or another. And so we  
12 wanted to make sure we prioritized the questions  
13 for them early on so we can get them all in  
14 before kids have to be picked up or what have  
15 you.

16 All right. Could we go ahead and have  
17 everyone introduce themselves? Even though  
18 Crystal has introduced herself previously, there  
19 are new faces in the crowd, so --

20 MS. ALLARD: Sure. I'm Crystal  
21 Allard. I'm the Director of the Division of  
22 Regulatory Science Informatics in the Office of



1 Science at CTP.

2 That means that I primarily focus on  
3 providing IT solutions for reviewers and other  
4 folks in the Office of Science. And I'd like to  
5 take one minute to pontificate on something I  
6 heard yesterday.

7 MR. CECIL: Pont away.

8 MS. ALLARD: Okay. Thank you. I  
9 heard something in one of the panel discussions  
10 yesterday that struck me as really interesting,  
11 and as a great example of why we're here and what  
12 we're doing today.

13 I heard that there is a perspective  
14 that potentially FDA is consistently moving the  
15 bar or changing the goal post for industry. And  
16 I think that's really interesting.

17 From my perspective, we're  
18 incrementally trying to share as much information  
19 as we appropriately can with you in order to get  
20 to meet the bar, right?

21 And so I think it's really helpful to  
22 hear that when we share information, you're

1 receiving it and that you're digesting it and  
2 that you have questions and that you are asking,  
3 because we are trying very hard to give you the  
4 information that you need in order to understand  
5 how you can help us help you do a thorough and  
6 efficient review. Thanks.

7 MS. STARK: Hi, my name is Cristi  
8 Stark. I am the Director for the Division of  
9 Regulatory Project Management. You guys will be  
10 interacting with many of my staff.

11 You'll see their names, numbers, and  
12 email addresses at the bottoms of your letters.  
13 Please use your RHPM as your liaison for  
14 clarifying questions, for clarifications on the  
15 review process, or any other information that you  
16 are seeking. We will do our best to write it  
17 down and get back to you if we don't have an  
18 answer on the phone. Thanks.

19 MR. JONES: Hi, I'm Glen Jones. I'm  
20 Deputy Director for Regulatory Management in the  
21 Office of Science.

22 And following onto some of the

1        comments Crystal just made, we are here to really  
2        try to be as transparent as possible.

3                Some of the presenters today have  
4        talked about rulemaking that's out there, some of  
5        it still for public comment, guidance documents  
6        we've published.

7                But we also want to do webinars, do  
8        meetings like this to answer your questions,  
9        because we're really trying to give you as much  
10       information in a variety of different ways as  
11       possible.

12               MS. KABARIA: Good afternoon. My name  
13       is Swati Kabaria. I'm one of the Deputy  
14       Directors in the Office of Compliance and  
15       Enforcement here at CTP.

16               I apologize. I have a prior commitment  
17       at 3:15 so I have to leave around then. But if I  
18       don't get to some of the questions that you have  
19       for me, you can always submit questions to the  
20       Office of Small Business, which is housed in the  
21       Office of Compliance and Enforcement, and we will  
22       get back to you. Thank you.

1 DR. MURPHY: Hi, I'm Iilun Murphy.  
2 I'm the Director for the Division of Individual  
3 Health Science in the Office of Science, and we  
4 focus on looking at the health impact of various  
5 tobacco products.

6 MR. CECIL: All right. Thank you very  
7 much. Let's go ahead and jump right in. We're  
8 going to try and get through all of these, and  
9 see if we can make it happen.

10 So, first question. Is an importer of  
11 bundled cigars that package them in the U.S. be  
12 considered a manufacturer?

13 MS. KABARIA: I can take that. So if  
14 I'm understanding the question right, the bundled  
15 -- are the cigars bundled? If the cigars are  
16 bundled in the United States after they are  
17 imported, then yes, that entity would be a  
18 product manufacturer, tobacco product  
19 manufacturer.

20 If the products are bundled outside of  
21 the U.S. and then imported, that entity would be  
22 an importer.

1 MS. STARK: I'm going to add one note.  
2 Many of these definitions are actually derived  
3 from our statutes, so if you look in Section 900,  
4 you will actually see the definition of  
5 manufacturer.

6 Within manufacturer, you will see  
7 there are two subtypes. One is the classical  
8 definition of manufacturer, where you will  
9 actively make, package, label your product. The  
10 other is an importer, so there has been some  
11 confusion regarding is an importer a manufacturer  
12 or not.

13 I want to note that importers are  
14 defined under that manufacturer definition in  
15 Section 900 of the Federal Food, Drug, and  
16 Cosmetic Act.

17 MR. CECIL: All right. Once FDA  
18 issues a PMTA order for a product, would Section  
19 301(tt) of the act prohibit the applicant from  
20 truthfully and accurately publicizing the FDA  
21 marketing authorization of the product, for  
22 example, via a press release or website

1 statement, even if the language used in the  
2 statement does not reference approval?

3 MS. KABARIA: So, Section 301(tt) of  
4 the Food, Drug, and Cosmetic Act prohibits  
5 statements that are directed to consumers that  
6 would mislead consumers that the product is  
7 approved or safe for consumer use or is endorsed  
8 by the FDA or is safer by a virtue of regulation  
9 by the FDA.

10 And we don't use the term approved  
11 when we're talking about authorizations of  
12 tobacco products. You can talk about your  
13 product as being authorized under the PMTA  
14 process, but 301(tt) would not prevent you from  
15 doing that.

16 MR. CECIL: All right. Where  
17 grandfather submission has been made but not yet  
18 determined, how should that submission be handled  
19 in the SE report?

20 Will the initial submission be  
21 reviewed, or does the new submission need to  
22 occur with the SE report?

1 MS. STARK: So I'm going to slightly  
2 reframe and just talk about some basic concepts.  
3 An SE report is one application type out of three  
4 to market a new tobacco product.

5 If a manufacturer is stating their  
6 product is grandfathered, meaning it was  
7 introduced or delivered per interstate commerce  
8 for commercial distribution in the United States  
9 on February 15th, 2007, that would not be  
10 something that requires any type of submission  
11 for a new product application.

12 This is part of the reason you've seen  
13 standalone voluntary grandfather determinations  
14 to help potentially if there are questions  
15 regarding that and to show evidence your product  
16 was out there.

17 If, however, you've modified that  
18 grandfathered product after that, and you're  
19 using that as a predicate, one of the things that  
20 would facilitate review during the SE review  
21 process is if you go through that standalone  
22 grandfather process first, have the evidence, and

1 then reference that STN as part of the SE report.

2 In the event that a manufacturer or an  
3 applicant has not yet done that, what will happen  
4 in the Office of Science is we will then send a  
5 request over to the Office of Compliance and  
6 Enforcement at the start of the SE review process  
7 stating, here's the predicate product, can you  
8 please take a look at the evidence and tell us,  
9 is it grandfathered or not.

10 MR. CECIL: All right. Great. The  
11 pile keeps growing while you're not looking.  
12 It's amazing. Tobacco Product Master File and  
13 grandfather products is the topic.

14 Could a Tobacco Product Master File be  
15 created for determined grandfathered products?  
16 This file would be referenced rather than  
17 submitting the previously submitted grandfather  
18 submission with the SE report, question mark.  
19 Can we just cross reference the GF STN?

20 MS. STARK: So as we discussed  
21 yesterday in the panels, the purpose of the  
22 Tobacco Product Master File is really when you



1 have information that you do not want the  
2 referencing applicant to look at, or for  
3 facilitating your review for multiple  
4 applications.

5 There was a question asked in the  
6 panel for putting an entire PMTA into a Tobacco  
7 Product Master File and we kind of beat around  
8 it, but we said there are certain things that  
9 don't really belong in the master file, such as  
10 samples.

11 Another example would be an  
12 environmental assessment, since that's for each  
13 product that's in there.

14 I'm going to look at a grandfather  
15 determination in the same manner. If you go  
16 through your voluntary submission and you receive  
17 a determination from the Office of Compliance and  
18 Enforcement that you are grandfathered, you'll  
19 see that there's a listing on the website that  
20 you could reference that you could place into  
21 your SE reports.

22 This is something that we're going to

1 allow for reference. You're not going to have  
2 all of the full materials in it. I want to note  
3 that the grandfather process, and I'll pass it  
4 over to Swati to discuss a little bit more, is  
5 through those STNs to allow for posting.

6 We will look at predicates, post that  
7 with part of our orders so people can see what  
8 they can reference. If it's part of the Tobacco  
9 Product Master File, people are not going to be  
10 aware of it, since those are protected. We do  
11 our best to have that firewall, again, for  
12 referencing.

13 So it's really in your best interest  
14 when you're looking at a grandfather type of  
15 submission to put that under a voluntary  
16 submission to the Office of Compliance and  
17 Enforcement.

18 MS. KABARIA: And I'll just add to  
19 that that the GF process through the Office of  
20 Compliance and Enforcement is merely a  
21 determination based on, you know, evidence that  
22 you submit, that your product was in fact on the

1 market as of February 15th, 2007, which is the  
2 grandfather date.

3 It doesn't include all of the detailed  
4 information that would be required for an SE  
5 determination, so that wouldn't be appropriate  
6 for a master file.

7 You would have to work with the Office  
8 of Science on the specifics of the requirements  
9 for SE to get the SE determination.

10 MR. CECIL: All right. This one was  
11 originally for Lillian, so what standards will be  
12 used for inspections for device manufacturers who  
13 frequently are only assemblers? How far down the  
14 supply chain will site inspections go?

15 MS. KABARIA: If this is in reference  
16 to a PMTA --

17 MR. CECIL: Yes.

18 MS. KABARIA: -- that's submitted,  
19 then we would be identifying the sites that we  
20 inspect through your application.

21 So you identify for us where your  
22 product is manufactured, and we would review and

1 determine which sites that we will visit as part  
2 of our PMTA review process. I'm sorry, I didn't  
3 get the other part of that question.

4 MR. CECIL: For device manufacturers  
5 who frequently are only assemblers for other  
6 parts that are received, how far down the supply  
7 chain do you need to go in your inspections?

8 MS. KABARIA: Well, that's going to be  
9 on a case by case basis. We review each  
10 application individually and we will review the  
11 information you submit and make a determination  
12 based on what you submit, where we will do our  
13 site manufacturing inspections.

14 MR. CECIL: Okay. A manufacturer has  
15 -- this is a hypothetical question, I imagine, a  
16 kit consisting of a closed tank containing an e-  
17 liquid and a proprietary battery.

18 They also sell a closed e-liquid tank  
19 and a battery separately. Crystal Stark stated  
20 the PMTA submission must contain the same  
21 subcategory. Would these products need to be  
22 filed under three separate filings?

1 MS. STARK: So we actually have a new  
2 motto. We're going to merge and become one  
3 character. You can see our names do merge to be  
4 Crystal Stark.

5 I'm going to start with identification  
6 of the products for submission, then I will turn  
7 it over to Crystal to talk about grouping for  
8 efficiency in an electronic submission format  
9 hopefully.

10 So when we're identifying products for  
11 potential authorization, we're looking at the  
12 actual product that a manufacturer is seeking.  
13 So what we're going to do is we're going to look  
14 at your battery that you're selling. We're going  
15 to look at your ENDS, your e-liquid in its closed  
16 cartridge.

17 Those two are going to be different  
18 products. They could be sold together. They  
19 could be sold independently. We're going to view  
20 it as, we're going to make a decision on those  
21 two, and if we say yes to those two, then it's  
22 going to be up to the company to determine how

1 they're going to package it and sell it out, but  
2 there's no need to submit it three different  
3 ways, each individually and then together.

4           When we're looking at the unique  
5 identification for these products, there are some  
6 questions, and this is where our project manager  
7 can come into aide for how you identify your  
8 product.

9           And when you go to look at our website  
10 for some of the policy memos, and I know Ms.  
11 Redus' talk also gave some websites where this  
12 unique ID memo is posted, you're going to see  
13 various categories and subcategories.

14           For some of these, it may not look  
15 reasonable to fill in the blanks. So if at all  
16 in doubt, you can call. You can always look at  
17 this as an ENDS component, but if you look at  
18 your battery, you're going to realize that there  
19 are other things that go into this, such as your  
20 watts or your amperes.

21           Give us that additional information,  
22 and then OS Can make a decision and a

1 determination for how that looks. You'll get  
2 that back in your acceptance letter from us if  
3 the application is accepted.

4 There's also the option to take a peek  
5 at some of the other items that have been placed  
6 on our website. We do try to update where  
7 applicable.

8 MS. ALLARD: Great. So when you're  
9 trying to determine what products you can group  
10 into a single submission to FDA, to CTP, there  
11 are four categories of information that we need  
12 you to consider.

13 The first one is, does it have the  
14 same manufacturer or importer? The second one  
15 is, is it the same application type? This means  
16 SE, PMTA.

17 And, pretend there are ands between  
18 all four of these, right, not ors, and is it the  
19 same product category, and is it the same product  
20 subcategory?

21 And when we say category and  
22 subcategory, we're very specifically referring to

1 the product ID memo. Commander Walters also  
2 mentioned it and included a link to it in his  
3 slides. I think it's in three separate slide  
4 decks.

5 You can also Google it. Google's  
6 really good at finding stuff. Google unique ID  
7 memo CTP, you will find it. If your products  
8 meet those four criteria, you can put them into a  
9 group submission.

10 I'm going to ask Todd a question. I  
11 know there was another question about grouping.  
12 Are we going to cover that later, or should I  
13 cover it now?

14 MR. CECIL: I'm not even sure where it  
15 is in the mélange here, so go ahead. Have at it  
16 now while you're thinking about it.

17 MS. ALLARD: Okay, great. So there  
18 were a couple of things about grouping that were  
19 asked in one of the questions.

20 One of them was, is there a limit to  
21 how many products you can group into a single  
22 submission, and the answer is no.



1                   When we first started trying to do  
2 estimates for how many products we knew were on  
3 the market, and I'm looking at Swati because we  
4 looked at these numbers together, it's somewhere  
5 in the range of one to maybe 600 million  
6 products, okay?

7                   And the idea of receiving all of those  
8 on the same day in May is terrifying for us. So  
9 if that means that we need to receive submissions  
10 with a very large number of products grouped by  
11 those four categories with the ands inserted in  
12 between them, we are prepared for that and our  
13 electronic systems will be ready to handle that.

14                   One of the best ways that you can  
15 enable us to receive those is to take a look at  
16 the slides that I shared with the example  
17 spreadsheet. The spreadsheet that I've presented  
18 on my slides was only a screenshot. My  
19 apologies. I couldn't get all of the columns.

20                   The second slide that I shared had, I  
21 don't know, 15 to 20 boxes. Each one of those  
22 boxes represents what could be a column in that

1 spreadsheet. If you provide that information to  
2 us for a large number of products, we will still  
3 be able to receive those and process them and  
4 review them. Thanks.

5 MS. STARK: So I'm going to use this  
6 opportunity for a little bit of discussion across  
7 the way here, when we're talking about electronic  
8 submissions and looking at very large numbers.

9 Well just look at ENDS liquids right  
10 now. And we're going to be all within the same  
11 manufacturer, same application pathway, we'll say  
12 PMTA, same category and same subcategory.

13 So I'm going to go with a closed e-  
14 liquid as an example. One of the other things  
15 I'm looking for is other types of things that you  
16 could submit electronically that would help  
17 facilitate FDA review.

18 I know that there are other items that  
19 we have out on our website, such as spreadsheets  
20 to assist with ingredient reporting that may be  
21 helpful. It may be helpful to know, I'm just  
22 looking at if there is UL certification, if

1 you're looking at your device or understanding  
2 coil temperatures if we're looking at that, if  
3 it's an entire closed system with a battery. I'm  
4 just looking at the options.

5           What are we willing to take here at  
6 FDA. Are we willing to take it all? Are you  
7 looking at test submissions where we could take a  
8 peek at this, or ways to have quick questions for  
9 child tamper resistance?

10           MS. ALLARD: Yes. So a lot of that  
11 information is helpful when supplied to us in a  
12 readily available electronic format, okay? So we  
13 are able to use that information and reuse it  
14 throughout the review when it's provided to us  
15 electronically in a format that we can read and  
16 review. Spreadsheets are good for that.

17           I would also say that I've received a  
18 couple of questions for a template for that  
19 spreadsheet and ideally, we would love to provide  
20 that at some point. Keep an eye on the website  
21 to see if we do, okay?

22           Just pay attention to what gets posted

1 on the website to see if we are able to provide  
2 more incremental helpful information about how  
3 you can provide us the information that we can  
4 use to review these types of submissions.

5 MR. JONES: I want to jump in at this  
6 point as well, because if you're going to, in  
7 fact, if you've got a large number of products,  
8 or even not so large, and if you're going to take  
9 advantage of that opportunity to group them  
10 together, Crystal has presented on the slide  
11 boxes that could represent columns of information  
12 to include.

13 But you could go beyond that depending  
14 upon what your product is and what type of  
15 information you're going to include in your  
16 application. You could, you know, put yourself  
17 in our position and think about what Crystal said  
18 in terms of the ability to take what's in the  
19 spreadsheet and use that to help the review team  
20 see what they're looking at.

21 So you could have columns for coil  
22 temperature and whether that coil temperature has

1 some type of a limit on it. You could have coil  
2 temps on there. Earlier in the day, I heard  
3 people talk about, you know, is the PG and the VG  
4 from a USB source? You could have a column in  
5 your spreadsheet that provides that information.

6 Earlier there were some comments about  
7 safety and product innovation and companies that  
8 might want to innovate with the products. You  
9 could have columns in your spreadsheet if, in  
10 fact, you have done innovation or you're, you  
11 know, if you have a flow restrictor, for example,  
12 you could have a column that makes it very easy  
13 for FDA to see up front that we put in place  
14 child resistant packaging or flow restrictors.

15 MR. CECIL: Swati, did you want to say  
16 something, or are you, all right. Good. All  
17 right. I have more questions. I was about to  
18 actually jump in and say let's go back to  
19 questions and make sure we get Swati out of here  
20 on time.

21 Okay. Another one for Lillian. If an  
22 unauthorized product is being sold on the market,

1 and the retailer is unaware that the product is  
2 unauthorized, can the retailer be penalized?

3 In other words, who bears  
4 responsibility, the retailer or the manufacturer,  
5 for unauthorized sales?

6 MS. KABARIA: Well, all of the above  
7 bear responsibility to ensure that they're in  
8 compliance with the requirements of the act. So  
9 the manufacturer bears responsibility in ensuring  
10 that they are not shipping adulterated or  
11 misbranded tobacco products into interstate  
12 commerce, and that includes products that don't  
13 have marketing authorization.

14 And the retailer bears responsibility  
15 to ensure that they're not selling misbranded or  
16 adulterated tobacco products. So I would say all  
17 of the above.

18 MR. CECIL: Okay, this one is a multi-  
19 part question, also for you. So I'll go one at a  
20 time. This is a fairly sizable chunk of text.

21 So would CTP consider the following  
22 new tobacco products requiring premarket review:

1 a filtered sheet wrapped combusted product that  
2 was commercially marketed prior to 2007, that has  
3 not been modified in any physical way, that was  
4 labeled as a cigar in 2007 and that was  
5 subsequently determined by a federal or state tax  
6 and authority to qualify as a cigarette and that  
7 is now labeled as a cigarette?

8 MS. KABARIA: So a grandfathered  
9 tobacco product is one that was on the market as  
10 of February 15, 2007, and I'm sure you all are  
11 aware of a recent court decision where the  
12 District Court of D.C. determined that  
13 modifications to the label of a tobacco product  
14 do not render it a new tobacco product if the  
15 contents within are unchanged.

16 So if your question is, the product  
17 itself is unchanged in any other way, then that  
18 product could qualify to be a grandfathered  
19 tobacco product, provided that you can submit  
20 that information when requesting that  
21 determination.

22 MR. CECIL: And would it be considered

1 to be a new tobacco product? Yes.

2 MS. STARK: I'm going to help with  
3 that, but with a little bit of clarification. So  
4 I want to note, when we're talking about the  
5 product, it's not just the physical product, it's  
6 also the container closure system around it.

7 So let me give you an example. I'll  
8 take a statutorily regulated product. So if you  
9 look at a pouched moist snuff, you're going to  
10 see that the container closure could be a tin.  
11 That tin could change from metal to plastic.  
12 That change in that metal to plastic, because it  
13 could impact characteristics, would render it to  
14 be a new tobacco product if it was modified after  
15 February 15th, 2007, in the United States.

16 The other thing I want to note is I do  
17 understand other agencies have definitions for  
18 how they label certain tobacco products and they  
19 differ from how FDA labels it.

20 What FDA is doing is we are viewing it  
21 based off of our definitions in our statutes. I  
22 can note that there are some differences when



1 we're looking at cigars versus roll your own.

2           So if you look at other agencies, they  
3 may look at the outer leaf when you're wrapping  
4 it and they may call that roll your own. When  
5 we're looking at our definitions here in our  
6 statute, that is going to be under the cigar  
7 category, not under the roll your own, because  
8 when we look at roll your own, we're looking at  
9 that final finished product going to the consumer  
10 and roll your own is following within that  
11 cigarette definition, which means it is wrapped  
12 in a substance not containing tobacco, which  
13 would automatically exclude that cigar leaf from  
14 that roll your own category.

15           So I want to make a note, even though  
16 other agencies may label something as a  
17 particular product, you need to pay attention to  
18 the categories here at FDA.

19           MR. CECIL: Okay. Next one. Okay.  
20 So now we have a tobacco filler product that was  
21 commercially marketed prior to 2007, has not been  
22 modified in any physical way, including

1 packaging.

2 Was labeled as pipe tobacco in 2007,  
3 has been determined since then to be called roll  
4 your own tobacco, and is now labeled as roll your  
5 own tobacco. Is that a new product?

6 MS. KABARIA: I think it would be a  
7 similar response, right? If the product itself  
8 has not been modified, if the container closure  
9 system, as Cristi correctly pointed out, has not  
10 been modified, if the contents within are exactly  
11 the same with no changes to the ingredients, the  
12 additives, the constituents, you know, what have  
13 you, then the product could, you know, qualify to  
14 be a grandfathered tobacco product.

15 MR. CECIL: I think the last one will  
16 fall in that same group. A tobacco filler  
17 product commercially marketed prior to 2007, not  
18 modified in any physical way, including  
19 packaging, was labeled as smoking tobacco  
20 suitable for use in a pipe or roll your own  
21 cigarette in 2007, and is now labeled as pipe  
22 tobacco.

1 MS. KABARIA: It's the same response.

2 MR. CECIL: All right. So that one  
3 was the last of the ones that have been  
4 identified as specifically and only for OCE.

5 There are others we would like your  
6 input on, but if you need to run, you're sort of  
7 off the hook-ish.

8 So let me jump to this one now.  
9 During the 10:45 session, and there's several,  
10 four of them, that have the same basic question,  
11 so I'll just read one of them.

12 Ms. DeBerry said that FDA is still  
13 considering comments on the proposed rule on the  
14 form and content of SE reports. Since the new SE  
15 report deadline is May 2020, six months away,  
16 will FDA be able to finalize the rule with enough  
17 time for us to follow it before the May 2020  
18 deadline?

19 MR. JONES: Unfortunately, we don't  
20 know. We're working very hard on a variety of  
21 documents. As the administration mentioned a few  
22 weeks ago, we're working on getting out things in

1 compliance guidance.

2 We're anxious to also try to finalize  
3 the SE and PMTA guidance document and rules as  
4 soon as possible. But at this point, we do not  
5 have an estimate for when that will occur.

6 MR. CECIL: All right. I already know  
7 what this one's coming back to. What is the  
8 minimum concentration of concern for potential  
9 vapors generated by heating in combination with  
10 all flavor ingredients?

11 All right. This seems to be a  
12 question of what is a minimum safe quantity? It  
13 is going to depend dramatically upon the material  
14 itself. We know that changes in carbonyls like  
15 formaldehyde at a nanogram level can have  
16 toxicity issues as can a change in benzene or any  
17 -- so the appearance of HPHCs even at relatively  
18 low levels are of concern and are of a level that  
19 is consistent with cigarettes.

20 So I think that when we talk about,  
21 what is the concentration of concern, it really  
22 does depend upon which individual HPHC we're

1 talking about. And there are always going to be  
2 toxicity issues related with flavors also.

3 So unfortunately, I can't give you a  
4 hard number. It depends upon what it is. Things  
5 like acrolein are present in 16 micrograms per  
6 cigarette, in traditional cigarettes. We see  
7 formaldehyde present at low levels as about a  
8 hundred nanograms in some cigarettes. And there  
9 is concern with toxicity there.

10 So I think it is important that you  
11 understand what is present in your aerosolized e-  
12 liquid and that it is reported. We clearly do  
13 not want to chase zero. We aren't saying there  
14 should be zero of anything at this point. We  
15 just need to understand what is there so we can  
16 understand what are the implications upon the  
17 public health.

18 Okay. Ms. Allard's modules suggest  
19 that there are three and only three literature  
20 review sections, non-clinical, clinical, and  
21 population health, which includes epidemiology  
22 and modeling.

1           Is that true across the board, meaning  
2           that a single all-encompassing literature review  
3           is not acceptable, nor is a set of several  
4           literature reviews, each of which ties to several  
5           topics described in the proposed rule, such as  
6           toxicology, human health risks, human factors, et  
7           cetera.

8           MS. ALLARD: I'm going to address this  
9           from the perspective of the intent of the eTTD  
10          Table of Contents and not the specific question  
11          about the literature review, because it's true  
12          for all of the sections within the eTTD Table of  
13          Contents.

14          The eTTD Submission Table of Contents  
15          is written to provide a means for organizing  
16          submission information for all application types,  
17          and therefore it is the responsibility of the  
18          submitter to look at those sections and determine  
19          where their information is relevant and where it  
20          should be included.

21          It does not work the other way. You  
22          should not be looking at the Submission Table of

1 Contents and then be deciding what you need to  
2 submit. You need to decide what you would be  
3 submitting otherwise, and then use that  
4 Submission Table of Contents to organize the  
5 information that you would have included anyway.

6 So if you're looking at literature  
7 references and there are multiple places for you  
8 to put that information, you need to look at what  
9 you're including and determine the relevance to  
10 the particular eTTD sections that are available  
11 to you and determine what information goes where.

12 In general, when we're talking about  
13 electronic submissions, it becomes beneficial to  
14 you and to us to provide information in more  
15 granular, smaller pieces, rather than one really  
16 big document or what have you.

17 The smaller they are, the easier they  
18 are to break out, and the easier they are to  
19 digest and to link to and to bookmark and to work  
20 through and to assign and to move through our  
21 systems.

22 So if you're trying to determine

1 whether or not we want all information in one  
2 huge document, or you would rather break it down  
3 into relevant sections, in general it is helpful  
4 when you break things down into the relevant  
5 sections.

6 If you have questions about where  
7 things appropriately belong within that eTTD  
8 Submission Table of Contents, you can submit your  
9 question to the eSub help desk and we can help  
10 get an answer. We work very closely with the RPM  
11 group and with Cristi's folks and with the eSub  
12 help desk to make sure that we're providing those  
13 answers for folks. We're happy to help.

14 MR. CECIL: Okay. And this one is, I  
15 will paraphrase. With small companies that have  
16 only \$1 to \$2 million to spend, will they  
17 actually be able to submit PMTAs and remain on  
18 the market with only one or two products? And is  
19 this enough money to be able to achieve a PMTA  
20 for even one product?

21 DR. MURPHY: I see eyes coming towards  
22 me. So we recognize that there are practical



1 limitations to, you know, manufacturers and what  
2 they can spend on pursuing analytical studies,  
3 clinical studies.

4 So depending on what your product is,  
5 we've talked about telling the story, right? So  
6 I think of each of these application submissions  
7 as, like a book, right? And there are chapters  
8 you need to fill to tell the story of your  
9 product and then for us to conclude that the  
10 product is appropriate for the protection of  
11 public health, looking at the totality of  
12 evidence.

13 So some manufacturers are going to be  
14 able to submit bigger books, a lot more detail  
15 than others. But, you know, you can have a  
16 smaller book but it could still be of quality,  
17 right? So I think that it is a business  
18 determination to decide what is the information  
19 available to you that is publicly available, what  
20 can you bridge to, and what are the important  
21 areas that, you know, you want to focus on on  
22 developing your own studies to fill the gap and

1 to tell us, you know, the, kind of totality of  
2 the information about your product so that we can  
3 understand the potential impact of marketing this  
4 product to consumers and non-users.

5 MR. JONES: Yeah, as Iilun said, it's  
6 a business decision. It's not one we can really  
7 probably help you a tremendous amount with.

8 But in some of the earlier comments  
9 you heard me talking about the need to do long-  
10 term, long-range planning. And so I would  
11 encourage you to think not only about what  
12 products and what applications and pathways, but  
13 also think about the long-term plan in terms of  
14 post-marketing studies, post-marketing  
15 inspections, post-marketing reports, and all the  
16 responsibilities you have if you make a regulated  
17 product.

18 MR. CECIL: All right. This question,  
19 similar. Given the 2020 deadline, if a company  
20 has not yet started analytical testing, HBHC  
21 storage and stability, et cetera, how likely is  
22 it they will be able to submit an application

1 that would be accepted and filed by the FDA or  
2 CTP, by the May deadline?

3 MS. STARK: I'll start, and then I'm  
4 going to ask others to help join in. So there's  
5 really, when you're looking at the PMTAs, three  
6 phases.

7 I want to note acceptance, we went  
8 through the criteria yesterday and they were in  
9 Ms. Busta's slides. It's pretty small. We're  
10 really looking at identification of product, have  
11 you actually submitted your environmental  
12 assessment, are there a few other items that are  
13 outlined? We have that refuse to accept rule and  
14 then we have some of the basics for the PMTA.

15 None of the constituent testing really  
16 plays a part for an acceptance determination.  
17 When we get to the filing stage under 910(b), we  
18 are going to be looking at product  
19 characterization. Part of that, we are going to  
20 be looking at constituent testing with it, so I  
21 am going to encourage you to take a peek at some  
22 of the other applications that we have taken

1 action on, some of the TPL reviews and other  
2 items, to see where we're at.

3 And the same thing for the substantive  
4 review. If you have not yet started planning for  
5 testing, you need to do that immediately. Did I  
6 cut out? It sounds odd.

7 Product characterization is going to  
8 be essential. Part of what we're looking at for  
9 the product is what goes in and what comes out.  
10 Look to see what you can gather from literature,  
11 publicly available material, where you can bridge  
12 if you don't yet have it.

13 There are a lot of helpful items that  
14 were presented yesterday and today with that. So  
15 I don't think that it is a non-option if you  
16 haven't started, but you really do need to take a  
17 peek at that, look at all the content that has  
18 been presented, take a peek at some of the  
19 guidances that are out there, take a peek at the  
20 proposed rule.

21 Please comment on it just to get a  
22 sense of what FDA is currently thinking for a

1       successful application. And while you're at it,  
2       read some of the technical project lead reviews  
3       out there summarizing some of the PMTAs that have  
4       been authorized so you have a sense of how FDA is  
5       viewing that.

6               MR. CECIL: And I would also add that  
7       testing doesn't necessarily need to take a long  
8       time. It will benefit you if you find a friendly  
9       statistician that can help you identify how to do  
10      design of experiments, how many replicates need  
11      to be done, and make the decisions and provide  
12      the information on why you made the decisions you  
13      made.

14              And that will tremendously reduce the  
15      amount of work that you have to do and how much  
16      you have to spend. So I'm not a statistician by  
17      training but maybe I should be.

18              All right. Next question. Long  
19      question. How will CTP provide a path or an  
20      avenue for small businesses that operate adult-  
21      only establishments and have been operated for  
22      nearly a decade?

1                   Thousands of smokers have  
2                   qualitatively reported a healthier lifestyle due  
3                   to changing from smoke to vapor. Let me get to  
4                   the question.

5                   Why is FDA asking each individual  
6                   company to conduct its own scientific research  
7                   and reinvent the wheel? There are four  
8                   fundamental ingredients in e-liquids, PG, VG,  
9                   nicotine, and flavor. Each of those ingredients  
10                  already have studies of their own.

11                  What is the likelihood that a PMTA for  
12                  e-liquids is accepted, having cited the research  
13                  results already conducted and including the  
14                  additional literature with pros and cons to  
15                  vaping as a smoking cessation alternative?

16                  MR. JONES: Well, first of all, we're  
17                  not asking people to reinvent what's already  
18                  known, but we are asking people to submit  
19                  applications for each individual product.

20                  The question started talking about  
21                  adult-only facilities, so from the retail  
22                  perspective, the retailers have a choice. Maybe

1 they've been making their own product. They  
2 might continue to do so. If that's the case,  
3 they're going to need to go through one of the  
4 regulatory pathways for that product.

5 Obviously, retailers have other  
6 options, too, to partner up with someone who's  
7 going to be the manufacturer for the product that  
8 they're going to sell within their facility.

9 DR. MURPHY: I would add also that  
10 there are factors that impact health impact,  
11 right? So for example, if you use the same e-  
12 liquid in one device versus another, the aerosol  
13 content may be different, right?

14 Also, even for the, you know, a  
15 particular device, depending on the use behavior,  
16 the health impact might be different.

17 So I think that there are, you know,  
18 as Hans Rosenfeldt provided earlier, there is  
19 many lines of evidence that would help us  
20 understand, what is the product and how is it  
21 being used, to ultimately understand the impact  
22 on the consumer.

1                   Because I think there is not just a  
2 simple, here is the e-liquid ingredients.  
3 Therefore, we should obviously be able to  
4 conclude what the impact on the individual will  
5 be, right?

6                   There are a lot of different things to  
7 consider. So I think it's important for us to  
8 therefore be able to connect all the pieces  
9 together and again, I use the phrase totality of  
10 evidence to understand ultimately the impact of  
11 the product when it's marketed and used.

12                  MS. STARK: I want to throw out one  
13 clarification as well. There was a term that was  
14 used in this question that actually does not fall  
15 under Chapter 9. That term was cessation. That  
16 actually falls to CDR, CVR, CDRH.

17                  When you look at statements such as  
18 treat, mitigate, prevent, cure, treatment, those  
19 fall under the Safety and Efficacy realm, and  
20 they would therefore not be under Chapter 9 for  
21 tobacco products.

22                  So we need to be careful with these



1 statements when we start to talk about cessation.  
2 This is something that we're going to look at  
3 from a jurisdictional process, and we're going to  
4 actually talk to CDRH or CDR or CVR appropriately  
5 for those sets of standards.

6 The other thing that I'm going to  
7 note, and maybe Todd can help a little bit since  
8 he is a chemist, is I know that everyone says  
9 there's only four ingredients, PG, VG, nicotine,  
10 and flavors. I want to note that there are  
11 differences with purity and grade for your PG and  
12 your VG.

13 There are different types of nicotine  
14 and flavors is many things. If you look at  
15 cherry, it could be 20 single ingredients, it  
16 could be 44 single ingredients, and depending on  
17 how it interacts with the container closure,  
18 leachables, everything else, you could be exposed  
19 to multiple items. So I want to note, it is not  
20 a simple four ingredients, if you'd like to add  
21 to that.

22 MR. CECIL: I think you said it

1 beautifully. There are not simply four  
2 ingredients. There can be as many as 50 or 100  
3 ingredients in a given e-liquid.

4 All right. Next one. Make sure there  
5 was no other comments there. How will FDA deal  
6 with new technologies that represent significant  
7 advances in harmless reduction versus previously,  
8 and I've edited, products that have previously  
9 received marketing orders, e.g., a new technology  
10 that renders IQOS obsolete? I didn't write it.

11 MR. JONES: We certainly encourage the  
12 industry to innovate for the reasons stated in  
13 the question. The application review process  
14 should not be a barrier to that innovation.

15 We described over these two days, in  
16 fact, for example, with the PMTA, you can send in  
17 an e-Ask request. After that, if you're making a  
18 minor modification to additives, you can send in  
19 a new PMTA, which has less information in it by  
20 cross referencing the original PMTA.

21 So innovation is really critical to  
22 the industry and to CTP's mission to try to move

1 people to less harmful products. As I mentioned  
2 earlier, there's certain types of innovation that  
3 we're all aware of, the general public is aware  
4 of.

5 For example, with problems with e-  
6 cigarettes catching on fire and exploding. We  
7 would encourage you, if you have a question about  
8 moving from a product that was on the market in  
9 2016 to one where you now want to have a UL or  
10 comparable battery standard, we would encourage  
11 you to reach out to the center, contact your  
12 RHPM, or send us a letter in terms of what you  
13 want to do so that we can try to work with you to  
14 get innovations such as battery standards in  
15 place.

16 Again, flow restrictors, other things  
17 you can do to address acute safety issues with  
18 the e-cigarette products.

19 DR. MURPHY: I wanted to add that we  
20 also have post-market reporting requirements that  
21 are attached to authorized products through the  
22 PMTA pathway.

1                   And that also is another tool that  
2 allows us to understand that a product continues  
3 to be appropriate for the protection of public  
4 health. So, you know, as the marketplace evolves,  
5 we're able to monitor that.

6                   MR. CECIL: All right. I have a whole  
7 bunch of questions from one person. I'm going to  
8 jump to somebody else's question and go back to  
9 them again. All right, are e-liquid containers  
10 required to have a specific resistance to impact,  
11 or will they be only required to be childproof?

12                  DR. MURPHY: I'm not familiar with any  
13 requirements that we have for impact resistance.  
14 But again, whatever container shape or design,  
15 product characteristics you choose, then you  
16 should tell us your justification and rationale  
17 for choosing that container closure system.

18                  And in terms of child protection, we  
19 recommend that it be child resistant. And again,  
20 there's more information on this in the ENDS  
21 final guidance.

22                  MR. CECIL: There are regulations in

1 DOT dealing with packaging stability. So I think  
2 all of that is covered by other agencies beyond  
3 FDA. Okay.

4 If the language from the proposed rule  
5 goes into effect written as is, do you agree or  
6 disagree that abuse liability and topography  
7 studies would be required for ENDS PMTAs?

8 DR. MURPHY: Well, that falls under,  
9 you know, my division, so I like information on  
10 abuse liability and topography. I think they are  
11 very helpful. As I said earlier, I think that  
12 health impact is a compilation of many different  
13 things.

14 So how an individual perceives and,  
15 you know, the appeal and perception of a product  
16 impacts use behavior, use behavior impacts your  
17 actual exposure to the product, thereby, you  
18 know, causing, you know, downstream health  
19 effects.

20 So I think that, for me,  
21 understanding, you know, what the topography is,  
22 what the use behavior is of a product, and

1 understanding the abuse liability are important  
2 aspects. But as we mentioned earlier, the  
3 proposed rule is just that, it's proposed, and  
4 it's available for comment.

5 And if there are other ways that  
6 people think that information can be provided so  
7 that FDA has sufficient information to understand  
8 the ultimate impact of a product being used,  
9 whether it's by the consumers or non-users, then  
10 we will consider that.

11 MR. CECIL: Let me restate this one  
12 slightly. If open system products have been  
13 surveyed to be predominantly used by adults  
14 quitting smoking, and closed pod systems have  
15 been shown to be fueling the youth epidemic, is  
16 there a framework or guidance possible to strike  
17 the difference between open system flavored ENDS,  
18 which are helpful to adults, and closed systems,  
19 closed pod systems that are detrimental to the  
20 health? Paraphrased.

21 DR. MURPHY: So we don't have any  
22 policies about closed versus open system

1 considerations at this time. Again, whether  
2 you're an open system manufacturer or a closed  
3 system manufacturer, we're asking you to present,  
4 again, the information, all the aspects that have  
5 been outlined in the proposed rule as well as the  
6 ENDS final guidance for us to understand the  
7 potential impact.

8 Certainly, among those considerations  
9 is the impact on youth and impact on current  
10 smokers and other tobacco product users. So  
11 these are all considerations that we are  
12 interested in you addressing.

13 MR. CECIL: Okay. Will this process  
14 include products that do not contain nicotine and  
15 are not electronic devices such as flavored or  
16 flavorless non-nicotine liquids?

17 MS. STARK: So I'm going to reframe it  
18 a little bit with just the concept of what FDA is  
19 looking at here. We are looking at products that  
20 are defined to be tobacco products.

21 We're going to be looking at  
22 components and parts that, when assembled

1 together, would classify under that definition.  
2 So while you may be selling a device independent  
3 of your cartridges, if it could be linked up with  
4 a cartridge that contains nicotine derived from  
5 tobacco, even though you're selling that device  
6 separately, that would be a component for a  
7 tobacco product.

8 Therefore, that would require, if it's  
9 new, an application to come in and be authorized  
10 so that you could sell in the United States.

11 We have had cases where we strictly  
12 have received applications or inquiries on  
13 applications for products that are not to be sold  
14 with anything derived from nicotine.

15 So with those, we do utilize a  
16 jurisdiction group across FDA centers to verify  
17 if it falls under the definition for a tobacco  
18 product or not. If there is a question, we  
19 encourage you guys to ask up front.

20 Please do not just assume, because you  
21 could very well have a component that is a  
22 tobacco product that would require you to follow



1 through the regulatory process as appropriate.

2 MR. CECIL: How will FDA consistently  
3 elevate newly deemed ENDS devices against the  
4 benchmark of APPH?

5 DR. MURPHY: Continue to elevate the  
6 benchmark?

7 MR. CECIL: Is that what, how will FDA  
8 consistently evaluate newly deemed ENDS devices.  
9 Sorry.

10 DR. MURPHY: Okay. Evaluate how we --

11 MR. CECIL: Sorry.

12 DR. MURPHY: -- consistently. Okay,  
13 well, we have one office director, Office of  
14 Science Director, who is currently the only  
15 signatory for the PMTA submissions.

16 So by nature of that process, there is  
17 consistency as best possible through, you know,  
18 making decisions. We do have a team of project  
19 leads that do the scientific evaluation of these  
20 applications.

21 And we do talk constantly and we do  
22 meet regularly to assess kind of the content of

1 these applications and trying to understand what  
2 the balance is in looking at the information to  
3 make the scientific determination that a product  
4 is appropriate for the protection of public  
5 health.

6 So I think that there are internal  
7 measures in place to try to be as consistent as  
8 possible across the scientific teams that come  
9 together.

10 MR. CECIL: If a major amendment to a  
11 PMTA is triggered due to the submission of  
12 additional final data from a clinical slash lab  
13 test, would this require the product to be pulled  
14 from the market if it is after the May 12th, 2020  
15 deadline?

16 MS. STARK: I'll start with this one.  
17 So when we're looking at the May 12th, 2020,  
18 deadline, what we're going to be looking at,  
19 first pass, is I'm going to be looking to see  
20 what have we received?

21 Did we receive it by 11:59:59 that  
22 night? Hopefully across portal, because we want

1 it to be electronic. She's smiling. If the  
2 answer is no, then we already know that those  
3 products would require prior authorization.

4 They shouldn't be marketed. If,  
5 however, we have received it, the applications  
6 have not received a refuse to accept or a refuse  
7 to file and later on there's a major amendment,  
8 we're looking in that one-year process right now  
9 and there hasn't been any type of negative action  
10 for them to come off the market.

11 If, however, we get to May 12th, 2021,  
12 we're going to have to talk about those cases at  
13 that point in time to see where are we with the  
14 review? What is it looking like?

15 This is where there may be some follow  
16 up with your regulatory health project manager  
17 with the status. I am pretty sure there will be  
18 some communication from the center regarding  
19 that, but we're going to have to look at those  
20 cases as we get there.

21 There is a large difference in what we  
22 consider major amendments. If we're getting a

1 major amendment for a brand new study with  
2 pivotal endpoints because nothing was submitted  
3 originally in the application, that may not be  
4 the best contender for us to look at in that case  
5 by case.

6 If, however, it may be something else  
7 to support some questions that FDA may have  
8 issued in a deficiency letter, that may be a  
9 different case. So we will have to look to make  
10 sure, one, do we have an active application in  
11 house, and two, where are we with the application  
12 and the contents within?

13 MR. CECIL: Okay. Again, I'll  
14 paraphrase this one. So if FDA banned e-liquids,  
15 it is very easy to make your own with PG, VG, and  
16 your own flavors and nicotine. How will FDA  
17 regulate this?

18 MR. JONES: FDA has not announced any  
19 plan to ban e-liquids, so I think the question is  
20 moot.

21 MR. CECIL: Okay. We may have  
22 actually covered this before. Assuming 400,000

1 SKUs get RTAs, how long after that date or the  
2 compliance deadline do retailers have to clear  
3 stock now slated for removal from the market?

4 MS. STARK: So Swati has unfortunately  
5 left due to other obligations. I'm going to note  
6 that when we're looking at the deadlines here,  
7 this goes to some of my past comments.

8 We're going to be looking, did we  
9 receive the applications by May 12th, 2020?  
10 After that date, we're looking to see, is there  
11 any type of negative action? One of those could  
12 be a refusal to accept. If that occurs after  
13 that date, those products no longer have an  
14 application in place. They are not taking  
15 advantage of those compliance policies.

16 There will be instructions associated  
17 with the letters. There should be communication  
18 coming out of CTP. And the Office of Compliance  
19 and Enforcement will assist with what we need to  
20 handle for any type of potential enforcement or  
21 other actions related to those products on the  
22 market with manufacturers and with retailers.

1                   So if this isn't the answer that  
2                   you're looking for, which it may not be, please  
3                   resubmit it through our Ask CTP so that we can  
4                   make sure that our colleagues in the Office of  
5                   Compliance and Enforcement can provide a little  
6                   bit more detail to respond.

7                   MR. CECIL: Okay. Product  
8                   characterization includes manufacturing  
9                   practices. So, one, how does the applicant  
10                  resolve the disconnects of the lack of GMPs or  
11                  TPMPs, and two, resolve the disconnect of  
12                  providing this information for products not on  
13                  the market? I can try.

14                  How does an applicant resolve the  
15                  disconnect of the lack of GMPs or TPMPs, and  
16                  resolve the disconnect of providing this  
17                  information for products that are not on the  
18                  market?

19                  MR. JONES: I think there may be a  
20                  point of confusion here. As you saw in some of  
21                  the presentations earlier today, manufacturing  
22                  practices, processes, validation, and consistency

1 is very critical piece of the product review,  
2 PMTA review process.

3 And so it's important for you to  
4 demonstrate through your application that you do  
5 have a controlled process for manufacturing.

6 The agency at some point will probably  
7 put in place TPMPs, Tobacco Product Manufacturing  
8 Practices. Those would be requirements that  
9 would apply to manufacturers of all products,  
10 including, for example, grandfathered products.

11 But the absence of those regulations  
12 or requirements at this time doesn't eliminate  
13 what a company needs to do if they're pursuing a  
14 product through the PMTA pathway.

15 MR. CECIL: Okay. I agree a hundred  
16 percent, by the way.

17 MS. STARK: I like to think of it in  
18 terms of a big picture concept. When we're  
19 thinking about a PMTA here, we're looking at, and  
20 Dr. Benson gets the credit for this, and Todd, I  
21 know that you stated it earlier. Tell us your  
22 story.

1           Part of that story includes how you  
2           make your product, your recipes, how you ensure  
3           it is the same product coming off the line, what's  
4           your target value, what are your specifications?

5           If you don't have this, or if we're  
6           starting to see information that's far outside of  
7           it, that may not be the same product, and that's  
8           really what we're asking for.

9           TPMPs, you look at GMPs and other  
10          centers. They help to get that consistency, that  
11          accuracy when it's coming across, but that's  
12          still part of your story to make sure right now  
13          when you're making that product the same thing  
14          that you intend to be sold to consumers is what's  
15          coming off your line. And that's really what  
16          we're looking for in these applications.

17          MR. CECIL: Upon submission of a PMTA  
18          or SE application for a deemed product, will FDA  
19          inquire whether the product is currently on the  
20          market and or request certification or  
21          documentation of the 8/8/16 marketing of the  
22          product?



1 MS. STARK: So I want to note for the  
2 compliance policy of August 8th, 2016, that is  
3 particular for products that currently require  
4 premarket authorization, that they can be  
5 marketed under this compliance policy if they  
6 follow certain items.

7 I want to note that this person asking  
8 the question might have some experience with  
9 provisional products where it was slightly  
10 different. So I'm going to kind of walk through  
11 a couple of definitions.

12 A provisional product was a tobacco  
13 product that was on the market. It's a new  
14 tobacco product, so it was in the U.S. after  
15 2/15/07, and an SE report was submitted by  
16 3/21/2011.

17 For those products, they are allowed  
18 to legally be marketed unless they receive an  
19 order that they were found not substantially  
20 equivalent. That's a little bit different than  
21 these deemed products under compliance policy,  
22 because these are not legally marketed. We just

1 have them marketed under the compliance policy.

2 With the provisional products, FDA  
3 went through a series of questions to verify that  
4 they truly were provisional, to make sure that we  
5 understood if they were legally marketed or not,  
6 because as we were going through the application  
7 process, we had to understand how to handle, when  
8 to post various other items associated with it.

9 With respect to the deemed products,  
10 there may be similar questions in the future  
11 depending on where we go and some of the  
12 notifications that we have to give to the public.

13 I want to note that in addition to any  
14 type of clarifying questions that may occur  
15 regarding products being on the market on  
16 8/8/2016, FDA may inquire for that through  
17 inspections.

18 So it may not be something formally  
19 coming from the Office of Science. It may be if  
20 you have individuals from the Office of  
21 Regulatory Affairs in tandem with Compliance and  
22 Enforcement and OS staff, out there for PMTA

1 inspection, during the inspection they may  
2 actually ask, can I see some of your evidence  
3 that your product was out there on this date?

4 So I just want to make sure people are  
5 aware that you may be asked at different points  
6 in time. In addition during that, they may ask  
7 for other types of regulatory requirements.

8 I want to note one of the other ones,  
9 and I mentioned it yesterday, was the requirement  
10 to submit ingredient listings. That applies for  
11 both foreign and domestic.

12 So please be aware of all regulatory  
13 responsibilities. Know that as manufacturers,  
14 you're required to comply with them and you may  
15 be asked at different points in time, so stay  
16 tuned.

17 MR. CECIL: All right. I want to  
18 modify this one a little bit, even though I think  
19 I know what the author was asking for.

20 So I have a cigar product, premium  
21 cigar, that's manufactured, is GF eligible, and I  
22 switched my source of tobacco from a field in

1 Virginia to a field in North Carolina. I made no  
2 other changes to my product. What is required  
3 for submission on May 2020?

4 MS. STARK: I will start and then I'm  
5 going to ask Todd, since you're our chemist, to  
6 assist. When we're looking at if you're a new  
7 tobacco product or not, I'm going to look at,  
8 have you modified your product?

9 And the short answer is, if you have  
10 not modified your product, then you could  
11 maintain your GF status. You have that GF  
12 status, but you would not be required to have an  
13 application.

14 The question is getting down to the  
15 tobacco itself, if that has changed. So there  
16 may be different types of tobacco, and I'm going  
17 to ask, phone a friend, I'm going to go to a  
18 chemist, since I'm not a chemist, to ask that.

19 But I'll make it really simple. I may  
20 change my tobacco itself. Let's just say that my  
21 leaf, I'll make it really easy. I'm going to  
22 change from burley to bright. That's a different

1 tobacco. That's a modification. That's a new  
2 product. I'm going to ask if you could help  
3 clarify a little bit further with this one for  
4 cigars.

5 MR. CECIL: We have not, to my  
6 knowledge, differentiated field to field, country  
7 to country, source to source, of tobacco leaves.

8 So a burley tobacco for the purposes  
9 of SE and PMT review, is a burley tobacco. A  
10 bright tobacco is a bright tobacco. So hopefully  
11 there's few changes being made to premium cigars.

12 Next question. All right. This is a  
13 slight deviation from that previous question.  
14 Child-resistant packaging.

15 It seems clear that open ENDS liquids  
16 would need to demonstrate child-resistant  
17 packaging. However, what about closed ENDS  
18 cartridges? Would they need to show child-  
19 resistant packaging? And what about pods?

20 MR. JONES: The issue here is acute  
21 nicotine toxicity, and so even with closed  
22 systems, there can be, and we've seen experience

1 with, leakage from some of those systems,  
2 including pods.

3 So the burden's really on the  
4 applicant to address the issue of nicotine, acute  
5 nicotine toxicity. And again, I'll go back to  
6 the issue of post-marketing.

7 It's probably better off, generally,  
8 if a manufacturer tries to anticipate problems  
9 rather than wait until after they've submitted  
10 the application and get it on the market and then  
11 face consequences such as recalls, vials  
12 breaking.

13 I know earlier there was a question  
14 about the glass and so forth. So this goes to  
15 good quality control and testing and making sure  
16 you have a robust product that's not going to  
17 subject users to nicotine leakage or other  
18 exposure.

19 MR. CECIL: Okay. I'm a manufacturer  
20 of cigar wraps. I sterilize them and I package  
21 them for sale. If my GF determination  
22 application is unsuccessful, how do I market my

1 product?

2 MS. STARK: So I just want to note  
3 that a standalone GF submission is voluntary.  
4 Part of the benefit for submitting it is making  
5 sure that you have the evidence and that you have  
6 a letter back from the Office of Compliance and  
7 Enforcement that you are grandfathered, because  
8 that's something easy to show if you have an  
9 inspection, that you have a product that can be  
10 legally marketed.

11 Otherwise, they may be asking for  
12 evidence to show that this is grandfathered. So  
13 I just want to keep that in mind. A standalone  
14 GF submission is not required. If the product is  
15 GF and you are complying with all of the other  
16 regulatory requirements, you should still be able  
17 to legally market your product.

18 If, however, you do not have the  
19 evidence and there's information to believe you  
20 have modified it since it's a new product and you  
21 do not have an order, you could be in violation  
22 of the act.

1                   MR. CECIL: Okay. This one is a  
2                   slighted change in tone, which is fun. There are  
3                   a lot of great questions raised at this meeting.  
4                   Will you be posting answers to those on your  
5                   website, including the questions that you've not  
6                   had time to answer today? That's it.

7                   MR. JONES: So I think we're going to  
8                   have a transcript of this session on the website.  
9                   The slides will be posted. I think we're trying  
10                  to answer all or most of the questions today.

11                  But you can continue to send in  
12                  questions including to Ask CTP. We will look  
13                  into the possibility of over time developing some  
14                  perhaps Qs and As or something to post on the  
15                  website.

16                  MR. CECIL: Thank you. Okay. Could  
17                  a cigar product on the market as of February  
18                  15th, 2007, that has only replaced the filler  
19                  tobacco because it is no longer grown or  
20                  available anywhere in the world, obtain GF  
21                  status? Would it be exempt from SE?

22                  MS. STARK: Okay, so if you modify



1 your product after February 15th, 2007, you're  
2 changing your blend, you're changing your  
3 percentages of your tobacco in there, that would  
4 be a new tobacco product.

5 The second question is, if you're  
6 changing the filler, could you go down the exempt  
7 from SE, that exemption request pathway, and the  
8 answer is no.

9 The exemption pathway is strictly for  
10 the addition, deletion, the increase or decrease  
11 of a tobacco additive. Tobacco itself does not  
12 work in that pathway, so you would need to look  
13 at either an SE report pathway or a PMTA.

14 If you have a grandfathered product,  
15 that would be a nice predicate to look at for the  
16 SE report itself. If you do not, then your other  
17 option is going to be a PMTA.

18 MR. CECIL: Which I think actually  
19 comes to this, the follow up question, which is,  
20 if the product receives a marketing order and the  
21 tobacco needs to be replaced in the future for  
22 the same reason, what should be done?

1 MS. STARK: So if we receive a  
2 marketing order, it's going to depend on what the  
3 order is for the appropriate pathway. And I'm  
4 going to just kind of repeat some basics so  
5 people have an idea, since there is three  
6 pathways to market.

7 You have the PMTA pathway, where you  
8 don't need any predicate. If you're authorized  
9 through the PMTA pathway and it's something  
10 that's minor, we can look at a supplemental PMTA,  
11 where you would cross reference and provide that  
12 bit of information in for determination from FDA.

13 If you have been authorized under the  
14 PMTA pathway, you are not eligible to go and use  
15 the SE pathway. That's because SE has a  
16 requirement with the predicate, it's either  
17 grandfathered or previously found SE.

18 You do have an option to utilize the  
19 exemption request pathway if you're making an  
20 additive change that is minor. So if you're  
21 changing the tobacco filler itself, that would  
22 not be appropriate for the exemption request

1 pathway.

2 When looking at the exemption request  
3 pathway, you can modify any legally marketed  
4 product. So that means you could modify  
5 something that was previously found exempt, where  
6 you've actually submitted your abbreviated report  
7 and placed it out there. You could modify  
8 something previously found SE. You could modify  
9 a pending provisional application, one that FDA  
10 hasn't reached a decision on and hasn't been  
11 found NOC. You could modify something authorized  
12 through the PMTA, as long as it is that additive  
13 change that's minor.

14 So again, tobacco itself is not going  
15 to be part of that pathway. For SE, you have two  
16 options for predicates. Your predicate is either  
17 going to be one that is grandfathered or one that  
18 was previously found SE.

19 think I hit all of them. Did I hit  
20 them all? Yes? Okay.

21 MR. CECIL: All right. I have a  
22 couple of connected questions here. We have some

1 roll your own related products that do not really  
2 fit into any other roll your own subcategories.

3 One, how do we categorize them? So  
4 far we've tried to find the best fit category.  
5 And two, what do we do if we don't agree with the  
6 category FDA has assigned the product? I'm  
7 mostly worried that we don't provide the  
8 necessary information if we categorize  
9 differently than the FDA.

10 Also, would there be an option to add  
11 a category, or should we utilize the Other  
12 category?

13 MS. STARK: Okay. I'll hit this,  
14 because this hits some of the earlier comments.  
15 I want to make sure that when we're looking at  
16 categorization, we're actually looking at the  
17 definitions from FDA and not from other agencies.

18 So when we're looking at the roll your  
19 own definition, I need to ensure that people are  
20 going to Section 900 of the FD&C Act and ensuring  
21 that it's appropriate. If they have questions,  
22 they can look at the policy memo online regarding

1 unique ID. They can also call a regulatory  
2 health product manager.

3 The one example that I gave earlier  
4 around a cigar leaf, that does not fall within  
5 the roll your own category. Roll your own is a  
6 statutorily regulated product category, and that  
7 is where we're looking at a final definition of  
8 cigarettes, where it is tobacco rolled in a  
9 substance that does not contain tobacco.

10 So I just want to make sure we're  
11 aware of that. If you have a novel product, and  
12 there are some out there, because our categories  
13 do not fit everything, we do have the Other  
14 category.

15 And the entire reason for having the  
16 Other category is to capture some of these  
17 products that are new and emerging that don't  
18 quite yet fit into some of the other, the cigar,  
19 the water pipe, the pipe, the ENDS, the  
20 cigarette, roll your own, and smokeless.

21 So we have actually had applications  
22 come in that utilize that. We are trying to take

1 record of that and see if we need to create a new  
2 category.

3           When submitting under the Other  
4 category, if you disagree with some of the  
5 categories FDA has, please provide your  
6 specification, but also please ensure we have  
7 that refuse to accept rule that you are providing  
8 all of the appropriate properties to identify the  
9 product.

10           All product categories for acceptance  
11 in an application are going to require that the  
12 manufacturer is identified, the product name is  
13 identified, the category, the subcategory, the  
14 package quantity, the package type, and the  
15 characterizing flavor.

16           If you don't have a characterizing  
17 flavor, we ask that you fill it out and state  
18 none. If you do have a characterizing flavor, we  
19 ask that you tell us what it is.

20           MR. CECIL: Great. Okay. This one  
21 has been identified as a question for Kim, but I  
22 think others have answers. You've got this.

1 Yes. She's here. She's hiding in the back. I  
2 see her.

3 If an EA is a standalone document,  
4 then why is an inadequate EA a reason for refusal  
5 to submit or a refuse to file? Particularly in  
6 other pathways, EX may generate an EA-based  
7 deficiency.

8 MS. STARK: Sure. So I'm going to  
9 actually attempt and I'm going to make sure that  
10 I'm looking at Dr. Benson that I get it right.

11 So the requirement for refusal to  
12 accept or refusal to file for the EAs actually  
13 stems from 21 CFR 25.15 and 21 CFR 25.40 and I  
14 kind of want to roll it out.

15 When CTP was added to the repertoire  
16 for FDA products, we actually went out with  
17 rulemaking regarding environmental assessments,  
18 categorical exclusions, and other types of  
19 environmental considerations, and with that we  
20 were added in to Part 25 that the rest of the  
21 agency is looking at.

22 When you look at the content for the

1 EA that is actually listed with the elements  
2 under 21 CFR 25.40. You then look earlier into  
3 the CFR for 25.15, and you're going to see that  
4 the agency actually could refuse to file if we  
5 didn't have an EA submitted in accordance with  
6 that, and we could also deny an application if we  
7 were missing certain elements associated with  
8 environmental considerations.

9 With respect to the SE program and the  
10 exemption request program, as we noted in earlier  
11 presentations today and yesterday, there is no  
12 filing stage. Because there is no filing stage,  
13 we are now looking at that under acceptance for  
14 21 CFR 25.15. So that's kind of where the  
15 authority is coming from.

16 You guys can read it if you don't  
17 believe me, and I'm going to see, I think I'm  
18 missing something so she's going to come up here.

19 DR. BENSON: I think some of what's  
20 holding things up here is the use of the term an  
21 adequate EA. And if you look at the National  
22 Environmental Policy Act and then the FDA's



1 regulations, it's very limited. It's kind of  
2 high level, what it's telling you to look at. It  
3 doesn't get into the granularity to have a very  
4 thorough EA.

5 So to have an EA that's adequate for  
6 acceptance for filing really just has a handful  
7 of things that it says you have to have that in  
8 there. But for it to be an EA that could support  
9 a finding of no significant impact, you're going  
10 to need a lot more detail.

11 So that's where you might have an  
12 adequate one to get accepted and filed, but then  
13 down the road, before you're going to be able to  
14 market because you have not addressed the  
15 environmental aspect of our major action, we  
16 might have more questions for you.

17 Hopefully the ones that are on the  
18 website and those of you with experience doing  
19 this with SE, they'll be very thorough and there  
20 may not be any questions as we go along.

21 But I think the trip us is an adequate  
22 EA. That sounds like sufficient EA, and it's

1 really not. It's the bare bar that is in NEPA as  
2 well as the FDA's regs.

3 MR. CECIL: Don't move. Wait.  
4 There's another one. So this is another multi-  
5 part question.

6 So new uses of e-liquids is likely to  
7 be coming from a competitor product in the same  
8 category, so other flavors of e-liquids. So is  
9 this category a category-wide comparator? So in  
10 the majority of cases, a comparator will be  
11 product with a largely similar risk profile. Is  
12 that an acceptable comparator for these products?

13 DR. BENSON: So I'll go back to Dr.  
14 Rosenfeldt's talk where he said, what is the  
15 right comparator? It all depends, right? Is  
16 there a, this is the comparator you should use if  
17 you want an e-cigarette as a comparator? No.  
18 There isn't.

19 Usually what we would say is, again,  
20 you know, you're telling the story, so tell me  
21 why you use that comparator. Give me your  
22 scientific justification. It's because these are

1 the users of the product or these are the people  
2 we assume will move to using this product. Or  
3 this is a product that's very similar in its  
4 ingredients and its risk profile. Or this is a  
5 large market share, so we want to get some of  
6 that market share, so we think that's a great  
7 comparator.

8 So what is the correct comparator?

9 Right now, there's a lot of factors in there, but  
10 it's on you to tell us the story of why this is  
11 the right comparator for you. And when I say the  
12 comparator, you could have several comparators in  
13 there. You're not limited to one.

14 MR. CECIL: And maybe one more. Yes,  
15 well, I'm pulling them all together since we've  
16 got you here. I'm taking advantage of it.

17 Could you tell us something about the  
18 expectations of the agency in terms of quality  
19 standards for the conduct of premarket population  
20 studies? Some are conducted based on market  
21 research standards, like other studies, like  
22 actual use, tried to apply the highest possible

1 standard, which often results in a mix of GCP,  
2 GEP, and ISO.

3 Same applies for data collection based  
4 on 21 CFR Part 11 compliance. Is that required?  
5 Data need to be submitted according to the CDISC.  
6 Thank you.

7 DR. BENSON: So --

8 MR. CECIL: If you insist.

9 DR. BENSON: The word population was  
10 in there, and I should identify, I'm the Director  
11 of the Division of Nonclinical Science, so humans  
12 and I don't really work together.

13 But I think at a high level, what that  
14 question is kind of about is, there are a lot of  
15 these guidances or best practices out there that  
16 govern studies that are usually done for the FDA,  
17 such as GLP, GCP, ICH, ISO, things like that,  
18 which by nature really, at least a lot of them,  
19 don't encompass the Center for Tobacco Products,  
20 at least not yet.

21 But does that mean they're useless to  
22 you? No. They aren't. So like GLP, I think

1       there's a draft out now that includes us, but  
2       it's not a requirement yet because we're not in a  
3       final rule there.

4               But would it benefit you to have any  
5       nonclinical study that you've done be done by  
6       GLP? It sure would. ICH, from a nonclinical  
7       standpoint, has lots of information on the proper  
8       way to conduct certain studies in toxicology.

9               Does that help you to follow that?  
10       Yes. It absolutely does. You might have to  
11       amend it a little, but saying it is primarily  
12       following ICH recommendations is hugely helpful  
13       to us. So I think although we're not absolutely  
14       in a lot of those regulations yet, are they  
15       helpful and can you follow them? Absolutely.

16               MR. CECIL: Iilun, do you want to add  
17       on?

18               DR. MURPHY: No, I echo Dr. Benson's  
19       thoughts. But basically, you know, if you follow  
20       standards that exist then it just strengthens the  
21       equality of the data that are produced.

22               And I would say that, you know, the

1 standards may be different for a focus group or a  
2 marketing survey versus a clinical study. And so  
3 for each type of study or analysis you're doing,  
4 I would encourage you to follow best practices.

5 Are there currently requirements for  
6 Center for Tobacco Products? No, but again, that  
7 doesn't mean that we don't encourage you to  
8 follow best practices.

9 MS. ALLARD: Can I add before you move  
10 on?

11 MR. CECIL: Yes, you can. I saw your  
12 name on that part, too.

13 MS. ALLARD: Yes. So unlike other  
14 centers, CTP doesn't have requirements for  
15 submitting clinical and nonclinical data in CDISC  
16 standards, which include SDTM and SEND for study  
17 data.

18 That doesn't mean that it's not  
19 helpful if you have data in that standard format  
20 and are able to submit it to us. It does enable  
21 us to do standard analyses using some of our data  
22 analysis tools.

1                   And we do work pretty closely with our  
2                   colleagues in other centers who use that data and  
3                   we share tools. So if you're interested in  
4                   submitting it, and you're concerned that it may  
5                   be problematic, I would say consider doing it  
6                   anyway and submit a question to our e-Submissions  
7                   help desk and we can help you with test  
8                   submissions, so that we can receive those types  
9                   of data files, and they do benefit our data  
10                  analysis when we receive them.

11                  DR. BENSON: I can't say we have  
12                  received things in the SEND format in my  
13                  division, and I had a handful of folks get  
14                  trained on it and now they haven't been using it,  
15                  so please send more so more people can get  
16                  trained on it and get used to using it.

17                  It is really helpful because it  
18                  generates things that otherwise we sit there and  
19                  have to enter data and generate ourselves.

20                  MR. CECIL: All right. Now, just for  
21                  a little housekeeping, we're going to go for  
22                  about 10 more minutes on the Q and A and then

1 we're going to start to bring this to a close.  
2 So those of you who are holding out and, you  
3 know, need a bio break at some point, we  
4 understand. We do have a few more minutes left,  
5 but I just want to give you a time check.

6 So all right. So we are conducting  
7 our CT and human factors using our six milligram  
8 per milliliter product at a 10 milliliter per day  
9 use, or a 60 milligrams per day. Does this level  
10 of use need to be on our labeling?

11 DR. MURPHY: So we don't have any  
12 requirements on the labeling. I think that if  
13 you have an intended use of your product and  
14 studies to support it, then we encourage you to  
15 describe that information and what we'll be doing  
16 when we receive it is we'll be looking to ensure  
17 that your labeling's not false or misleading and  
18 if we agree with the information that's there,  
19 then it would be authorized accordingly.

20 MR. CECIL: All right. FDA said that  
21 the comparative products should be legally  
22 marketed. As we understand that there are no



1       legally marketed ENDS products, can the applicant  
2       pick a comparator product without knowledge of  
3       even if the company is making a comparator  
4       product, will submit a PMTA?

5               DR. MURPHY: Do you mind repeating the  
6       question again?

7               MR. CECIL: I can try. The FDA stated  
8       that comparator products should be legally  
9       marketed. As we understand there are no legally  
10      marketed ENDS products, can the applicant pick a  
11      comparator product without knowledge of even if  
12      that company will be making a comparator product  
13      as a submission to PMTA?

14              DR. MURPHY: Okay. So we don't have  
15      any legally authorized ENDS products available at  
16      this time. However we know that consumers are  
17      able to purchase many ENDS products. So if you  
18      are planning to submit an ENDS PMTA and looking  
19      for comparators, sure, you know, use whatever  
20      available information is out there.

21              So I think that one could consider,  
22      you know, if you have a closed system, what are

1 the top most popular brands, whether it's the top  
2 five or top 10, and you can use that grouping as  
3 your comparator basis.

4 If it's an open system, again, what  
5 are the most popular products that are similar to  
6 yours that would be an appropriate comparator and  
7 what available information is there?

8 There are a lot of studies that have  
9 been done to date and will continue to accumulate  
10 more scientific information. And clearly they  
11 tend to, you know, study most popular products  
12 that are being used.

13 So I think that, you know, use what's  
14 available even if you don't have all the specific  
15 information because you're not the manufacturer.  
16 I think use the available information that you  
17 have at your disposal and bridge as best possible  
18 to the comparator products to let us know why you  
19 think that this is an appropriate comparator.

20 What information do you have to be  
21 able to compare based on broad categories. Even,  
22 like, what are the flavorings? What is PGBG?

1       What are the diluents? What is the nicotine  
2       concentration? You know, if it's open, or if  
3       it's an e-liquid, what are the devices that are  
4       typically used?

5               So there's a lot of considerations but  
6       you can try to specify as best you can but we  
7       understand that there are limitations.

8               MR. CECIL: Another comparator  
9       question. Again, I'll paraphrase this one. I'm  
10      making an e-liquid. What's my comparator  
11      product? Do I compare it to tobacco filler? And  
12      if that's the case, am I comparing the filler  
13      HPHCs to the e-liquid HPHCs? Or am I trying to  
14      find some other comparator product?

15              DR. BENSON: So I would go back to Dr.  
16      Rosenfeldt's slides where he showed that there  
17      could be an application for an ENDS product, so  
18      it could just be an e-liquid, that the right  
19      comparator there is a cigarette. Or it could be  
20      the right comparator is another e-liquid. So it  
21      would just depend on the application.

22              MR. CECIL: Okay. If I sold a RYO

1 tobacco on February 15th, 2007, and now sell a  
2 very similar product but market it as a pipe  
3 tobacco, will the FDA allow me to file and the  
4 FDA review an SE application as the two tobaccos,  
5 or only slightly different would be deemed to be  
6 from cross categories?

7 Yes, this one was, let me try. If I  
8 sold a RYO tobacco before 2007, and now sell a  
9 very similar product that's marketed as pipe  
10 tobacco, can I use the one that was sold in 2007  
11 as a predicate for an SE?

12 MS. STARK: Okay so, I think this goes  
13 to reading of the proposed SE rule as well, where  
14 we talked about predicates within the same  
15 category or using predicates outside the  
16 category.

17 Currently we do not have any finalized  
18 rule implemented in place for the SE program. So  
19 as of today, an adequate predicate is going to be  
20 what you deem with the content in your  
21 application to support that, meaning you have a  
22 predicate that was grandfathered and you are

1 going to state what the differences in  
2 characteristics are between that grandfathered  
3 product or the one previously found SE and your  
4 new product.

5 If that means your grandfathered is  
6 RYO filler and your new one is pipe filler,  
7 currently without any type of rule in place,  
8 because I know what was proposed, we did limit  
9 the categories, that is applicable.

10 I do know that the comment period for  
11 the SE rule has closed. We're reviewing those.  
12 We're going to try to have content come out as  
13 soon as possible but as of today, there is no  
14 requirement regarding a predicate being in the  
15 same category. So that is applicable to do.

16 MR. CECIL: Okay. Can you change the  
17 name of a product that is subject of a PMTA order  
18 without submitting a supplemental application?

19 MS. STARK: A change in a name is not  
20 a new tobacco product. So therefore, you would  
21 not need to submit a supplemental PMTA for this.  
22 And it's not just for a PMTA. It's also if

1 you're changing the name for something that was  
2 authorized under the SE pathway or the exemption  
3 request pathway.

4 I will note there are other  
5 requirements that you need to be aware of as  
6 well. If you look under Section 905 for  
7 registration and product listing, we're looking  
8 for the listing of your products and your  
9 associated labels and advertisements associated  
10 with it, so you may need to make updates for  
11 that.

12 If you have post-market reporting  
13 under your PMTA and you're changing your name,  
14 that would be a nice thing to tell us as part of  
15 the post-market reporting. But I do want to note  
16 that just a change in name is not a new tobacco  
17 product.

18 MR. CECIL: Does the PMTA review  
19 process distinguish between products for  
20 inhalation versus products for oral application  
21 based on the obvious difference and potential  
22 risk? Does the PMTA review process differentiate

1 between?

2 DR. MURPHY: So we consider again the  
3 totality of the information and the route of  
4 exposure is a consideration. But we look at many  
5 different aspects. We look at, you know, the  
6 likelihood of initiation of a product, the use  
7 behavior, switching behavior, poly-tobacco use  
8 behavior, the toxicological risk profile, what we  
9 know about the health impact.

10 So I think that depending on what it  
11 is and the route of exposure, along with all the  
12 behavioral aspects, I mean, again, we consider  
13 many, many different parameters of the product  
14 and kind of overall make a determination that  
15 allowing the product to go to market would be  
16 appropriate for the protection of public health.

17 DR. BENSON: I can say  
18 toxicologically, obviously, route of  
19 administration matters, right? And so you could  
20 have a chemical, an ingredient in two different  
21 products that would be fine via one route from a  
22 toxicity standpoint, but via another route very

1       problematic.

2                   Either, you know, transformation of  
3       something that you use orally in your liver that  
4       ends up making a toxic metabolite or something  
5       that you're inhaling and going directly at the  
6       lung and it has some lung toxicity or you're  
7       heating it and inhaling it and now you have brand  
8       new chemicals forming that wouldn't have formed  
9       if you were taking the product orally.

10                   So obviously from our side in the tox  
11       world, that's a huge issue. So obviously we  
12       would look at those differently.

13                   MR. CECIL: Okay. And again, this one  
14       I'm going to paraphrase slightly. Just received  
15       a last-minute text. And let me read to you  
16       what's here first, and then I want to modify.

17                   So what products are required to  
18       submit a PMTA by May 2020? We've answered this a  
19       couple of times, but I think it's nice to be  
20       abundantly clear.

21                   Does this include cigars and hookahs?  
22       I think if we were to be a little bit clearer



1 what needs to be submitted by May 2020? Not just  
2 PMTA, but also SE or EX.

3 MS. STARK: When you're looking at the  
4 compliance policy and the timelines with the  
5 recent ruling, we're looking at deemed tobacco  
6 product applications for new tobacco products.  
7 So I'm looking at cigars, pipes, water pipes,  
8 ENDS, Other, for those ones that fit in that  
9 Other bucket that may not fall under any of  
10 those.

11 So if you have a new tobacco product  
12 that is in the deemed category with a compliance  
13 policy, a product application will need to be  
14 submitted.

15 There are three options for  
16 applications, a PMTA, an SE report, or an  
17 exemption request. And I want to note, it's not  
18 submitted, it's receipt by CTP's Document Control  
19 Center, and there is a difference.

20 We have had things lost in the mail,  
21 and if they come in a month later, you may miss  
22 that date. This is why we're looking at our

1 portal, our electronic submissions. You don't  
2 have to worry about holidays. You don't have to  
3 worry about snowstorms or hurricanes, because our  
4 servers are open and can receive at horrible  
5 hours in the morning when most people are asleep.

6 So I'm going to encourage electronic  
7 submissions for all new product applications. If  
8 it is not a new product, meaning it was  
9 grandfathered, there is no requirement for an  
10 application to be submitted.

11 So that means if your deemed tobacco  
12 product was introduced or delivered for  
13 interstate commerce for commercial marketing in  
14 the United States, as of, meaning on February  
15 15th, 2007, that is a grandfathered product that  
16 is not new, there is no requirement for an  
17 application to be submitted.

18 However, if you introduce your product  
19 in the U.S. after that date or you modify that  
20 product after that date, with our compliance  
21 policy, FDA should be receiving a product  
22 application by 11:59 p.m. on May 12th, 2020.

1                   And I want to note it is our Document  
2 Control Center here in CTP. If it goes to a  
3 different Document Control Center and takes a few  
4 days to get over, it's when our CTP DCC receives  
5 it.

6                   So again, look on our website for our  
7 address, our operating hours for physical mail  
8 delivery, and obviously use our portal for  
9 electronic submissions.

10                  DR. CECIL: This is the rapid fire  
11 round. You have four questions left. All right.  
12 And I think we can answer these pretty quickly  
13 with perhaps one word on some of these.

14                  So, how does OS intend to conduct its  
15 review process for the PMTA submitted by May 2020  
16 given the court mandated one year for review and  
17 decision or requirement for removal of products  
18 from the market?

19                  Does CTP intend to expedite review in  
20 any way? Yes. Okay next.

21                  MS. STARK: We're prepared to receive  
22 and review and make timely decisions. What would

1 be, what would increase our efficiency is  
2 ensuring a complete application upon receipt.

3 MR. JONES: And also, if you're going  
4 to group submissions using something like a  
5 spreadsheet, like Crystal talked about, would  
6 really help us get access to that data more  
7 quickly.

8 MS. ALLARD: Yeah. And the more  
9 electronic information we receive, the better  
10 able to automate the process further down in the  
11 review process we are, right.

12 So, if we're looking for efficiency,  
13 paper, paper does not support that.

14 DR. CECIL: Next one is, unfortunately  
15 I know this one, who answers this one, when  
16 should we expect the 2017 amendments to the one  
17 side of t-test memo for the equivalence  
18 comparison of HBHC data to be published on the  
19 FDA website?

20 I did not know that it was not posted  
21 yet. But do we have a time-line for its posting?

22 MR. JONES: So, this question is

1 referring to a website where we've got several  
2 cites, policy memos posted, those, we referenced  
3 those I think during an earlier presentation.

4 We're going to continue to try to get  
5 more documents up on that website. I don't have  
6 a specific time frame, but just within the last  
7 few days we've put up, I think, a couple more  
8 cites, policy memos and some other documents  
9 which we call reviewer guides.

10 These documents were also written to  
11 assist the FDA reviewers with doing their  
12 reviews.

13 So the, you know, if you look at the  
14 website you'll see there's appropriate disclaimer  
15 language indicating that these documents  
16 represent our current thinking at a point in  
17 time.

18 I know earlier there was mention that  
19 some of those documents were written a few years  
20 ago.

21 Those memos certainly might change and  
22 get updated at some point at some point but

1 you're welcome to look at those and monitor that  
2 website for any future additions.

3 DR. CECIL: All right. And then there  
4 were two. The scientific review policy memos are  
5 very useful. Can FDA please post one for how SE  
6 reports should be tailored for premium cigars and  
7 their unique characteristics?

8 MR. JONES: So, I don't think we have  
9 that memo yet, but if we, if we develop such a  
10 memo for the FDA review staff then we would try  
11 to post it.

12 DR. CECIL: Last one. For ENDS  
13 products what is the requirement or  
14 recommendation to test the effect on nonusers of  
15 secondhand smoke exposure?

16 DR. BENSON: Obviously not any  
17 requirement for it and I really feel like that's  
18 one of the things that you don't necessarily have  
19 to specifically test for, right.

20 So, if you are characterizing the  
21 aerosol and you know the potential for exposure  
22 that way, you could address the nonuser exposure

1 to second and third hand aerosol through that.

2 I don't see that it's something that  
3 requires separate testing.

4 DR. CECIL: All right. With that, I'd  
5 like to say thank you to the panel. You help up  
6 well.

7 There are, we do have a couple more  
8 speakers to close the meeting out and I'll give  
9 you a chance to find your seats and we'll ask  
10 Brittani Cushman to come up and offer her closing  
11 remarks.

12 (Applause.)

13 MS. CUSHMAN: All right. Thanks  
14 everybody for your time yesterday and today. A  
15 big thank you to FDA, CTP and the personnel who  
16 are both here in the room and online for your  
17 time, for your preparation for this workshop.

18 Industry is extremely appreciative of  
19 these types of events because as one of my  
20 colleagues would say, FDA is a contact sport and  
21 what I mean by that is not football or flag  
22 football but the more contact we have, the more

1 both sides learn about the process.

2 We have seen significant progress in  
3 the flow of information with regard to both SE,  
4 PMTA and of course the SE exemption pathway,  
5 whether it be the proposed regulations, the final  
6 PMTA guidance, the scientific policy memos.

7 This workshop and I would also note  
8 other engagements that FDA personnel participate  
9 in, the industry basing-type workshops that are  
10 out there, we greatly appreciate your  
11 participation in those.

12 And we know you're not required to do  
13 that but we greatly appreciate the interactions  
14 there. All that being said, we, I would say,  
15 have some continuing issues that I'll just  
16 highlight a handful of those based on what we've  
17 talked about today.

18 Several people associated with FDA,  
19 maybe not those in the room, but continue to say,  
20 you know, why have manufacturers not completed  
21 these applications, why have they not been filed.

22 And I would say, you know, just like



1 you all were receiving this information  
2 incrementally and we want to make sure that we're  
3 submitting high quality, complete applications as  
4 best we can.

5 And for us that behooves us to get as  
6 much information we can for as long as we can  
7 prior to putting those applications in.

8 One example of that, that we learned  
9 about yesterday was some information that Crystal  
10 highlighted on some better ways of providing the  
11 formatting for applications.

12 And I think for many of us in the room  
13 perhaps that was the first we've seen of the  
14 modular approach and perhaps putting it in that  
15 format versus some of the methods and Tables of  
16 Contents we've seen previously.

17 And I know at least for my company and  
18 for others, we've been working forward on the  
19 previous way of looking at the Table of Contents  
20 versus this modular approach.

21 So, while that's not perhaps  
22 substantively changing our process for

1 application, it is a very time consuming way of  
2 reworking what we're putting together to try to  
3 put it in the best, most complete method for you  
4 all to review.

5 The other issue that I would highlight  
6 that came up in the past two days was this idea  
7 of minor versus major amendments and trying to  
8 delve into what that means and what the  
9 differentiating point is between those two.

10 And I'll talk about it a little bit  
11 more in a minute but in terms of just timing, you  
12 know, I look at it is it better for a company to  
13 get something on file that perhaps isn't entirely  
14 complete and then make some sort of unsolicited  
15 amendment later.

16 Would that amendment be considered  
17 minor or major and if a major solicited amendment  
18 were to be submitted later on, what does that do  
19 to our 12-month timeline if you have two 180-day  
20 periods that you're looking at back to back. Let  
21 alone if you add in any processing time in  
22 between.

1           So, the other issue, I actually heard  
2           some chuckles in the room, it may have been the  
3           only time I heard a lot of people laugh, which  
4           was, there was the suggestion that we should have  
5           a pre submission meeting 12 months in advance of  
6           our filing.

7           And considering the May 2020 deadline  
8           is not 12 months away and I don't have a time  
9           machine I certainly was one of the people in the  
10          room that laughed a little bit at that and I  
11          understand the spirit behind, which is, you know,  
12          you should get it as early as possible to have a  
13          pre submission meeting.

14          But I think it is a little bit of an  
15          acknowledgment of, you know, how difficult this  
16          process is that you would need to have a pre  
17          submission meeting at least a year in advance.

18          And I hope that gives some sympathy to  
19          those at the agency in terms of what those of us  
20          in the industry are going through to try to  
21          continuously be building the plane while we're  
22          flying it in terms of getting our applications

1 in.

2 So, you know, obviously I could give  
3 a number of examples and I think my industry  
4 colleagues did a great job of providing, you  
5 know, some questions and some things for the  
6 agency to think about on a number of these points  
7 and other points.

8 But I'd like to close out by looking  
9 at how to look at this going forward and  
10 particularly in light of some of the comments  
11 made in the Maryland lawsuit about, from the PMTA  
12 standpoint for ENDS, it's not a good idea to  
13 clear this market of a large number of the  
14 products that are out there from a public health  
15 standpoint.

16 And so, a few things that I took away  
17 from this was that perhaps unsolicited amendments  
18 are going to play a big part in the applications  
19 given the short runway we have before filing.

20 I believe that this would be in the  
21 interest of both FDA, who will want complete high  
22 quality applications and industry who want to

1 provide you with complete high quality  
2 applications and simply may not be able to do so  
3 in the time frame before us given that we're  
4 still learning about this process.

5           Companies may be able to file  
6 applications that are, you know, perceived to be  
7 in process with time-lines for completion of the  
8 various elements of the application and later  
9 supplemental filings or amendments or, you know,  
10 whatever nomenclature you'd like to use for that.

11           And I'd look at that as similar to how  
12 previous iterations of the extension requests  
13 were handled, which was to say we're working on  
14 this, this is the time-line we expect and this is  
15 the rationale for why we need this time-line.

16           And, you know, looking at the six  
17 months we have before us ahead to May 2020, I've  
18 talked to a number of the lab vendors and the  
19 consultants that work on these projects and I can  
20 tell you from the industry perspective, we're  
21 beginning to hear that they're just not accepting  
22 clients anymore.

1                   And so, for those trying to continue  
2                   to fill out their application, and I use the term  
3                   fill out from the standpoint of, make them more  
4                   complete, you know, we're running into the  
5                   barriers of just finding places to get a lot of  
6                   this work done.

7                   Or we're finding that we're needing to  
8                   supplement what the studies are and when we go to  
9                   them they say well, you're going to the back of  
10                  the line or we no longer have the ability to add  
11                  that onto your study.

12                  So, those are just a few things that  
13                  we're running into and I would, you know, remind  
14                  everyone that those who have products on the  
15                  market today, we're facing the proposition that  
16                  we may file something and if it's deemed to not  
17                  be complete, we're having to pull those products  
18                  from the market.

19                  And we're not likely to be bankrolled  
20                  to go back and try again. The fact of the matter  
21                  is that from a manufacturer's standpoint our  
22                  respective approaches may change again from how

1 they look today based upon the publication of the  
2 final guidance policy that we expect to be coming  
3 out with regard to flavored products.

4 And companies will have an even more  
5 difficult decision to make as to whether to  
6 continue to navigate this process or to simply  
7 give up due to the complexity cost or the  
8 shifting landscape before us.

9 I think in many cases that would be a  
10 shame both from the standpoint of the industry  
11 but also from the standpoint of offering lower  
12 risk alternatives to adult smokers and continuing  
13 to encourage industry to provide those  
14 alternatives.

15 Going forward enforcement will become  
16 of utmost importance. Good actors cannot  
17 function in a market where bad actors are allowed  
18 to proliferate in the absence of strong  
19 enforcement.

20 We as an industry continue to deeply  
21 and sincerely appreciate FDA's efforts to provide  
22 information and feedback and to improve these

1 processes and we hope that the flow of  
2 information can continue going forward.

3 Thank you all for your time, for your  
4 efforts and for the productive conversations the  
5 past two days and hope you enjoy the rest of your  
6 day.

7 DR. CECIL: Thank you very much, and  
8 for the final closing remarks, let me turn to  
9 Julia McGinn-Rodriguez.

10 MS. MCGINN-RODRIGUEZ: So, there are  
11 a few still left in the room, thanks for holding  
12 out. We really wanted to make this as meaningful  
13 and enriching an experience for you as possible.

14 So, I want to thank our colleagues  
15 from CTP for extending their time with us through  
16 later today and for really engaging with the  
17 audience.

18 As well as for those who served on the  
19 panel with us from industry and those who  
20 submitted questions to us in advance of the  
21 meeting in person and by phone.

22 It really allowed for us to have as



1 much information flow as possible and to  
2 Brittani's point to really help facilitate this  
3 contact sport. We were greatly looking forward  
4 to this opportunity to provide as much meaningful  
5 information to you as possible.

6 I would just like to quickly recap  
7 from the first day in the morning there are a  
8 number of resources that were provided and the  
9 Redus provided, the presentation provided by Ms.  
10 Redus.

11 You're going to want to look back at  
12 those links to just familiarize yourself with a  
13 number of different resources that we have on the  
14 website.

15 Ms. Allard, who spoke after that,  
16 presented later, had a lot of tips in terms of  
17 some of the digital resources that are available  
18 to you as well. Just a CliffNotes version of  
19 some of the suggestions she had if you want to  
20 take advantage of those.

21 You know, making use of eSubmitter,  
22 the Portal, testing your submissions early,

1 submitting your IAM requests at least a couple of  
2 weeks in advance because that can take a little  
3 bit of time.

4 And then check back in later also for  
5 updated, an updated version of the textback  
6 document because we anticipate that we'll be  
7 updated that and if you check frequently you'll  
8 be able to see newer iterations of that.

9 And she'd also mentioned that there's  
10 an RSS feed and I just want to plug that so you  
11 can actually sign up. It's a subscription basis  
12 on the different pages where you want to have an  
13 opportunity for automated updates to monitor any  
14 changes that are occurring on the website.

15 So I had actually asked for, I was  
16 just out of curiosity, how many questions we had  
17 received and actually answered in this short two-  
18 day session.

19 So, during the panels and advance of  
20 the senior leadership meeting, panel hearing we  
21 had 81 questions that we answered, which I find  
22 gratifying because it really gives us an

1 opportunity to address as much as of the input  
2 that we're receiving from the public as possible.

3 If you have outstanding questions,  
4 again you can reach out to your regulatory health  
5 project manager or the Call Center, CPT's Call  
6 Center, Office of Small Business, Office of the  
7 Ombudsman.

8 If you don't know where to go, you can  
9 address general questions to [askctp@fda.hhs.gov](mailto:askctp@fda.hhs.gov).

10 So, in summary I'm not going to keep  
11 you any longer, thank you so much for your  
12 thoughtful engagement and great questions. This  
13 concludes our Fall public meeting.

14 (Whereupon, the above-entitled matter  
15 went off the record at 4:33 p.m.)

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17  
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## A

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C E R T I F I C A T E

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In the matter of: Deemed Tobacco Product  
Applications: Public Meeting

Before: US FDA

Date: 10-29-19

Place: Silver Spring, MD

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/Neal R. Gross/  
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**NEAL R. GROSS**

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