

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.

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. 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.

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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C E R T I F I C A T E

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Applications: Public Meeting

Before: US FDA

Date: 10-29-19

Place: Silver Spring, MD

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