

FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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TOBACCO PRODUCT APPLICATION REVIEW
PUBLIC MEETING

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TUESDAY
OCTOBER 23, 2018

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The Public Meeting convened at the
Hilton Washington DC/Rockville Hotel and
Executive Meeting Center, 1750 Rockville Pike,
Rockville, Maryland, at 8:30 a.m.

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

2 (8:31 a.m.)

3 MS. RUDOLPH: Thank you. Good
4 morning, everyone. My name is Karin Rudolph.
5 I'm with the Stakeholder Relations Office here
6 for the FDA Center for Tobacco Products. Welcome
7 back to our meeting -- our public meeting, Day 2.
8 We have a big day in store for ourselves. Three
9 special sessions to be able to cover some
10 additional important topics.

11 As a reminder, when we get started
12 with our panels, we've been able to provide all
13 of our outside speakers with the opportunity to
14 introduce themselves and have five minutes to
15 address the content of interest that they want to
16 address related to the sessions.

17 To get us started this morning, we're
18 going to go ahead and move right into our --
19 let's see -- our session, which is Session 6.
20 And we're going to talk about -- Matt Walters
21 will talk about content focus, request for
22 exemption from substantial equivalents. And then

1 Colleen Rogers and Todd Cecil will talk about SE
2 report content. Thank you.

3 MR. WALTERS: Good morning. I'm
4 Commander Matthew Walters. And I will be
5 discussing the exemption request pathway,
6 focusing on scientific content. I'm currently
7 the deputy director within the Division of
8 Product Science, Office of Science.

9 Just to give you the key information
10 as far as what I'm going to be discussing this
11 morning, I will be going over some of the key
12 regulatory information that just reminds --- what
13 we talked about yesterday, information to include
14 the exemption request submissions, examples of
15 possible exemption request modifications, and
16 examples of why FDA has issued some Refuse-to-
17 Accept letters.

18 Just to orient everyone and remind
19 everyone about the definition of a new tobacco
20 product, I've put the definition up here, as this
21 will be very important as I talk about this
22 information this morning, as well as other

1 presentations as we move throughout the day.

2 As Jennifer mentioned yesterday, I
3 just want to go over briefly what --- the final
4 rule for the exemption request pathway, which
5 became effective on August 4th, 2011. As Jennifer
6 mentioned yesterday, an exemption request must
7 include the following information: a detailed
8 explanation of the purpose of the modification; a
9 detailed description of the modification; a
10 statement whether the modification involves
11 adding or deleting a tobacco additive; a
12 statement as to whether this modification is also
13 -- involves increasing or decreasing the quantity
14 of existing tobacco additives; whether the
15 modification is minor; why an SE report is not
16 necessary; and an environmental assessment.

17 The exemption request submissions are
18 limited to additive modification only as defined
19 in Section 900 of the FD&C Act. I've just
20 provided the definition here for review.

21 The exemption request submissions from
22 a scientific standpoint have been limited to two

1 disciplines; typically a chemistry review and
2 environmental science review. The exemption
3 request submissions tend to be very short, 20 to
4 25 pages not including the environmental
5 assessment that's also required for these
6 submissions.

7 Information that would facilitate
8 FDA's review of the exemption request pathway and
9 submissions include: providing the applicant
10 contact information; a table identifying unique
11 identifying properties of the new and original
12 tobacco products, as well as the eligibility of
13 the original tobacco product; a statement
14 identifying the commercial eligibility of the
15 original tobacco product; and the intended
16 marketing status of the new and original tobacco
17 product if an exemption order is issued.

18 Here's an example that would
19 facilitate FDA's review in identifying the unique
20 identifying properties of the new and original
21 tobacco product. Such an example here for
22 cigarettes, identifying the length, diameter,

1 ventilation, and characterizing flavor.

2 In addition, to facilitate FDA's
3 review and statement of the proposed
4 modification, a statement of the purpose of
5 proposed modification, a description of the
6 proposed modification as needed, explain why the
7 modification is minor, and why these
8 modifications do not alter the characteristics of
9 the tobacco product. A table that compares
10 between the new and original tobacco product
11 identifying the additives is helpful to
12 demonstrate this. A discussion justification of
13 why an SE report is not necessary. And as I
14 mentioned before, an inclusion of the
15 environmental assessment is needed.

16 As required in the rule, a minor
17 modification statement and purpose is required
18 for these submissions. In the example I proposed
19 here are some examples of which an applicant
20 could make these statements. For example, an
21 applicant could state a proposed minor
22 modification being made is to delete additive A

1 or add additive B, increase the quantity of the
2 existing additive C, or decrease the quantity of
3 existing D.

4 For the purpose of providing a
5 statement for the purpose of the proposed
6 modification, an applicant can provide a
7 statement stating: delete additive A and add
8 additive B due to a change in supplier; or
9 increase additive A and decrease additive B due
10 to state compliance mandates; or delete additive
11 D due to additive D no longer being commercially
12 available. These are just some examples of which
13 an applicant can provide such statements to the
14 FDA in exemption request submissions.

15 Often some exemption modifications
16 that may be appropriate for this pathway may
17 include: change in additive quantity of the same
18 additives from different sources if grade and
19 purity are identical; change in additive quantity
20 of different additives with same function if
21 grade and purity are identical; change in
22 additives in packaging that are not expected to

1 impact the properties of the tobacco product;
2 replacement of non-FSC cigarette paper with FSC
3 cigarette paper; removal of complex additives or
4 flavors such as going from a mentholated
5 cigarette to a non-mentholated cigarette; and
6 addition or deletion of additives found in a
7 tobacco product component.

8 Some examples that may not be
9 appropriate for the exemption request pathway
10 include: product design modifications, as these
11 are not additive changes only; tobacco blend
12 modifications; and significant packaging changes
13 that would affect the characteristics of the
14 tobacco product.

15 As I mentioned, FDA has issued a
16 number of Refuse-to-Accept letters for this
17 pathway. Many of the reasons that we've issued
18 such letters include the following: modifications
19 are not limited to change in additives, such as
20 tobacco blend changes; failure to submit
21 exemption requests in an electronic format;
22 failure to provide key information including

1 environmental assessment, purpose of the
2 modification, information indicating where the
3 modification is an increase/decrease of existing
4 additives, or adding or deleting an additive,
5 information demonstrating original product
6 eligibility, full identification of new and
7 original tobacco product, and an explanation of
8 why the modification is minor and why an SE
9 report is not necessary.

10 In conclusion, applicants have
11 improved in recent years as applicants have
12 become more familiar and more experienced with
13 this pathway. The applications are better
14 organized, there's a clear link between the
15 information provided and the regulatory
16 requirements, improved explanation of why a
17 modification is minor and why an SE report is not
18 necessary. FDA has also been able to meet its
19 performance goals for this pathway. However, we
20 welcome any feedback in this area.

21 And finally, I'm going to turn it over
22 to my colleagues, Dr. Rogers and Dr. Cecil, as

1 they'll be talking about scientific review of SE
2 reports.

3 MS. ROGERS: Good morning. I'm Colleen
4 Rogers, Director of the Division of Product
5 Science in the Office of Science. This morning,
6 Dr. Cecil and I will jointly present information
7 on SE report content. The presentation will cover
8 SE report content and deficiencies that CTP
9 frequently finds in SE reports, and our
10 recommendations for how to address those
11 deficiencies.

12 All right, first I'll start with an
13 overview of SE report content. Okay. As you
14 heard yesterday, the FD&C Act requires that
15 before a new tobacco product can be introduced
16 into interstate commerce, it must undergo pre-
17 market review by FDA. One of those pre-market
18 review pathways is a submission of a report under
19 Section 905(j), otherwise called a substantial
20 equivalence or SE report.

21 An SE report is intended to
22 demonstrate that a new tobacco product is

1 substantially equivalent to a predicate tobacco
2 product. When we refer to the SE report, this
3 includes the initial submission, as well as any
4 amendments. Since 2010, FDA has received more
5 than 5,000 pre-market tobacco product
6 applications, most of which have been SE reports.

7 An SE report should contain the
8 following information in general: a unique
9 identification of both the new and predicate
10 products; evidence that the predicate tobacco
11 product is grandfathered or previously found SE;
12 a summary that contains a brief description of
13 the specific similarities and differences between
14 the new and predicate products; and, where
15 applicable, the grandfather product.

16 A comparison of the characteristics of
17 the new and predicate products. Section
18 910(a)(3)(b) of the FD&C Act defines
19 characteristics as the materials, ingredients,
20 design, composition, heating source, or other
21 features of a tobacco product which also includes
22 the presence of harmful and potentially harmful

1 constituents or HPHCs.

2 Reports should contain testing
3 information on the characteristics of the new and
4 predicate products. Also, a statement of
5 compliance with applicable tobacco product
6 standards; a health information summary or a
7 statement regarding the availability of such
8 information; and as you've heard already, an
9 environmental assessment or a valid claim of
10 categorical exclusion.

11 In the next few slides, I provide some
12 examples of the types of information that has
13 facilitated FDA's review of SE reports. For
14 example, it has been helpful to provide a side-
15 by-side listing of tobacco types and sub-types in
16 a table, which also includes the units of
17 measure, target values and ranges for each
18 tobacco type, and a description of the tobacco
19 grading system. It's also helpful to provide the
20 amount of each component in reconstituted tobacco
21 in a separate table.

22 It has facilitated our review of SE

1 reports when the report provides a side-by-side
2 listing of all ingredients in a table, which also
3 includes the CAS number, function, unit of
4 measure, target value and range. Similarly, it
5 facilitates our review to list all design
6 parameters in a table, which includes the target
7 and range values for each design parameter and
8 the units of measure. It is also helpful if the
9 new and predicate products use the same units of
10 measure for each parameter.

11 Some other items that are helpful and
12 facilitate our review include: a side-by-side
13 listing of ingredients in each component in a
14 table; providing the quantity of each ingredient
15 expressed as a mass per unit of use, such as
16 milligram per cigarette; a listing of every
17 difference in characteristics with an explanation
18 of why, despite those differences, the products
19 are substantially equivalent; providing all cited
20 references, preferably in an appendix rather than
21 throughout the body of the report; and it's
22 helpful to provide your submission

1 electronically.

2 Now I'll describe some of the common
3 deficiencies that we have seen in SE reports and
4 our suggestions for how to address those
5 deficiencies. The first group of common
6 deficiencies are related to issues with predicate
7 tobacco products. The first common deficiency is
8 when the predicate tobacco product is no longer
9 available. All SE orders are based on a
10 comparison of the new tobacco product to a
11 predicate tobacco product. Therefore, data on
12 the predicate tobacco product are important for
13 our review. If a manufacturer no longer
14 manufactures the predicate tobacco product or it
15 is no longer available, the manufacturer still
16 needs to fully characterize that predicate
17 product. And if the characteristics are different
18 from the new product, explain why the differences
19 do not cause the new product to raise different
20 questions of public health.

21 Data on the predicate tobacco product
22 may be requested to demonstrate that the new

1 tobacco product is substantially equivalent. FDA
2 has frequently encountered SE reports that lack
3 full predicate tobacco product characterization
4 because the predicate tobacco product is no
5 longer available.

6 If the predicate tobacco product is no
7 longer available, FDA has suggested a couple of
8 potential options to manufacturers. One option
9 is to re-manufacture the predicate tobacco
10 product at present day, consistent with the
11 product, composition, and design specifications
12 in place at the time the predicate product was
13 originally manufactured. In this case, FDA has
14 requested design parameter data and documentation
15 demonstrating that the manufacturer of the
16 predicate tobacco product at present day is
17 reflective of the predicate product at the time
18 of original manufacture.

19 Where any differences exist between
20 the present day predicate, product design
21 parameters, components, or constituents and the
22 original predicate product, it's helpful to note

1 those differences. FDA has generally considered
2 a present day predicate tobacco product that
3 differs from the original product to be a
4 surrogate tobacco product. And I'll speak more
5 about surrogate products in a moment.

6 Another potential option is to
7 identify a different, currently available tobacco
8 product that has design parameters, components,
9 and constituents similar to the predicate
10 product. This tobacco product generally will be
11 considered a surrogate tobacco product. It would
12 be helpful to note any differences between the
13 surrogate predicate and the original predicate
14 product as far as design parameters, components,
15 or constituents.

16 Similarly, if a manufacturer uses a
17 predicate tobacco product that they do not own,
18 the manufacturer still needs to characterize that
19 predicate product. If the manufacturer does not
20 own the predicate tobacco product, it would be
21 helpful to submit an explanation of the means by
22 which they obtained the information that was

1 submitted, and a certification that they have
2 access to the product composition information
3 from the predicate tobacco product manufacturer.

4 In some cases, a surrogate tobacco
5 product may be used to supply test data for an SE
6 report. What is a surrogate tobacco product? A
7 surrogate tobacco product is neither the new or
8 predicate product. They can be used for the
9 predicate product, the new product, or both.
10 They generally have design parameters,
11 components, and constituents similar to the
12 tobacco product it represents.

13 A remanufactured predicate tobacco
14 product that is identical to the original
15 predicate product is not considered a surrogate
16 product. Data for the surrogate tobacco product
17 are provided in place of data for the new or
18 predicate product when those data are not
19 available. For example, an SE report for a
20 cigarette may include HPHC data for a surrogate
21 predicate tobacco product because the applicant
22 no longer makes the predicate product, but

1 manufactures the surrogate product and therefore
2 can analyze it for HPHCs.

3 In this example, the SE report could
4 include tobacco blend information for the
5 predicate and surrogate predicate products
6 demonstrating that the products have identical
7 blends, that is, identical tobacco and additives.
8 The applicant could indicate that because of the
9 identical blends, tobacco-specific nitrosamine
10 filler data for the surrogate predicate product
11 can be extrapolated to the predicate product.

12 FDA must evaluate whether data from a
13 surrogate tobacco product can be extrapolated to
14 the new or predicate tobacco product. If there
15 are insufficient data to justify using the
16 product as a surrogate, FDA cannot make an SE
17 determination using those data. FDA has received
18 SE reports where, for an example, an applicant
19 used a surrogate tobacco product for which HPHC
20 data were to be extrapolated to the newer
21 predicate product. However, the SE report did
22 not include the target specification or tobacco

1 blend for the surrogate product, and did not
2 indicate which product the new or predicate was
3 to be compared to the surrogate. This information
4 is important for FDA to be able to determine
5 whether it's appropriate to use surrogate data.

6 If your report includes a surrogate
7 tobacco product, the following information would
8 facilitate our review: a description of which
9 tobacco product the surrogate product represents;
10 a justification for using the surrogate product
11 in lieu of the predicate or new product; a
12 detailed description of all ingredients and
13 design parameters for the surrogate product;
14 surrogate test data that is to be extrapolated to
15 the tobacco product it represents, as well as the
16 test procedures and method validation reports for
17 those data.

18 The second set of common deficiencies
19 that we see are related to ingredient review
20 issues such as incomplete ingredient listings,
21 inadequate rationale for changes in ingredient
22 quantities, and incomplete tobacco processing

1 information. SE reports should include
2 information on product ingredients that enables
3 us to compare the new product with the predicate
4 product. We have encountered SE reports that
5 included information on some, but not all product
6 ingredients, or reports that did not fully
7 identify the ingredients, such as not providing
8 information on tobacco grade, ingredient grade,
9 or purity.

10 We see SE reports that provide
11 quantities as percentages, rather than measured
12 amounts with the units of measure, or reports
13 that contain discrepancies among different
14 sections of the report in the quantities or types
15 of ingredients. Further, we've seen SE reports
16 that did not fully identify complex ingredients
17 such as the flavoring mixture or casing, or did
18 not provide the single ingredients -- excuse me --
19 - or the single ingredients provided for a
20 complex ingredient did not add up to 100 percent.

21 It would facilitate our review to
22 provide the following information for each

1 tobacco product: the ingredient names, absolute
2 quantities, and functions for all components;
3 uniquely identifying information for all tobacco
4 types; uniquely identifying information for all
5 ingredients added to tobacco; the single
6 ingredient names and absolute quantities in each
7 complex ingredient. I note the complex ingredient
8 also includes reconstituted tobacco. The quantity
9 of each ingredient expressed as mass per unit of
10 use, rather than providing them as percentages.

11 Ingredients that are not single
12 chemical substances or single types of leaf
13 tobacco are considered complex ingredients. It
14 would facilitate our review to distinguish
15 between complex ingredients made to your
16 specifications and those that are not. If a
17 complex ingredient is made to your
18 specifications, provide complete information
19 according to FDA's guidance for industry on
20 listing of ingredients in tobacco products.

21 If a complex ingredient is not made to
22 your specifications, FDA requests that complete

1 information on the single ingredients that make
2 up the complex ingredients be provided. If
3 applicable, we suggest that you work with your
4 supplier to submit a tobacco product master file
5 for the complex ingredient.

6 It would facilitate our review if the
7 SE report explains why any change such as
8 increase, decrease, addition, or deletion of an
9 ingredient does not cause the new tobacco product
10 to raise different questions of public health.
11 We have encountered SE reports that did not
12 address differences in ingredient quantities
13 between the new and predicate products. We've
14 also seen reports that did not make a comparison
15 between the ingredient quantities of the specific
16 new and predicate products that were subject of
17 the SE report.

18 SE reports should provide an adequate
19 explanation of the impact of ingredient changes
20 on public health for the new tobacco product.
21 They should account for the potential toxicity of
22 the changed ingredient via the route of exposure

1 to users. For example, buccal exposure for an
2 oral tobacco product or inhalation exposure for a
3 cigarette. Reports should account for the
4 potential effects of the changed ingredients on
5 HPHC delivery. For example, combustion of the
6 ingredient and its impact on HPHC yields in a
7 burning cigarette.

8 FDA has not found the following
9 explanations of the impact of ingredient changes
10 to be persuasive: a statement that the
11 ingredients have been used at similar levels in
12 other tobacco products, or statements that the
13 ingredients are acceptable because they are used
14 as flavors in food when the ingredient will be in
15 a product that's combusted.

16 If your newer predicate tobacco
17 product contains fermented tobacco or is heat-
18 treated, it would facilitate our review to
19 provide information about the fermentation or
20 heat treatment process. These treatments can
21 result in differences in the chemical
22 constituents of the tobacco, as well as impact

1 the microbial content of the final product. We
2 have encountered SE reports that did not specify
3 whether the tobacco has been fermented or heat-
4 treated. In those cases where it was identified
5 that the tobacco was fermented or heat-treated,
6 they did not provide details of the processing
7 conditions.

8 It would facilitate our review to
9 provide the following information for each
10 tobacco product that contains fermented tobacco:
11 the duration of fermentation and fermentation
12 conditions such as the pH, temperature, and
13 humidity; microbial characterization data of the
14 fermentation inoculum or starter culture if one
15 is used; ingredients added during the
16 fermentation process that would impact the
17 microbial stability of the product if it's
18 applicable; any methods used to stabilize or stop
19 fermentation if one is used; and the storage
20 conditions of the final product prior to
21 packaging.

22 It would facilitate our review to

1 provide the following for each tobacco product
2 that contains heat-treated tobacco: the type of
3 heat treatment that was used; the process
4 parameters; any validation information for the
5 process; and an explanation of why any
6 differences in processing do not cause the new
7 tobacco product to raise different questions of
8 public health.

9 The third group of common deficiencies
10 are related to reporting of constituents such as
11 nicotine and HPHCs.

12 Because nicotine is an addictive
13 component of all tobacco products, comparative
14 data for this ingredient is important to allow us
15 to make a determination of the potential impact
16 on public health. It would facilitate our review
17 to provide the following information for each
18 tobacco product: data on the total nicotine yield
19 based on at least three measurements; if they're
20 different, it would be helpful to provide
21 evidence to demonstrate that the increase or
22 decrease in nicotine yield does not cause the new

1 tobacco product to raise different questions of
2 public health with respect to addiction.

3 HPHC information is usually necessary
4 to provide a complete comparison between the new
5 and predicate products and make an SE
6 determination. We have encountered SE reports
7 that provide HPHC data, but fail to include
8 sufficient testing information, such as:
9 providing HPHC data for the predicate tobacco
10 product; providing the quantitative methods used
11 or the testing laboratory accreditation; not
12 providing standard deviations; or not providing
13 complete data sets for all tobacco products, or
14 the method validation parameters.

15 It would facilitate our review to
16 provide HPHC testing for both the new and
17 predicate products. Consider measuring those
18 HPHCs that would be impacted by the differences
19 in tobacco blend ingredients and product design
20 of your new and predicate products.

21 For cigarettes, it's helpful to
22 evaluate mainstream smoke produced by the new and

1 predicate products under both ISO and Canadian
2 intense smoking conditions. For smokeless
3 tobacco, it's helpful to evaluate extracts of the
4 new and predicate products. If there are any
5 differences between the testing methods carried
6 out for the new and predicate products, it would
7 facilitate our review to identify those
8 differences and explain why the data for the new
9 and predicate products can be evaluated despite
10 the differences.

11 It would facilitate our review to
12 provide the following information for each
13 tobacco product. Complete data sets for all
14 tobacco products including the following: a
15 summary of the results for all testing performed;
16 the number of replicates tested; standard
17 deviations; and referenced product data sets. It
18 would also help our review to provide a complete
19 description of the quantitative test protocols
20 and method used, which include: the testing
21 laboratory and their accreditation; method
22 validation status and validation reports and data

1 for each analytical method; the length of time
2 between the dates of manufacture and dates of
3 testing; and the storage conditions prior to
4 initiating testing.

5 We suggest that appropriate measures
6 be taken to minimize data variability and
7 systematic bias in HPHC testing. The suggested
8 measures include using the same laboratory and
9 methods, using the same type of smoking machine
10 if applicable, testing within a similar time
11 frame, and using similar sample storage
12 conditions and duration. If the test methods
13 that you're using are national or international
14 test standards and there are any deviations from
15 those methods, it would be helpful to provide
16 information about those deviations.

17 It's important to include stability
18 information for the following types of tobacco
19 products because the manufacturing process,
20 storage conditions, and length of time on a shelf
21 can affect their characteristics: smokeless
22 tobacco products and products that contain

1 fermented tobacco.

2 We have seen SE reports that failed to
3 provide full stability data, such as: not
4 providing stability data over the entire shelf
5 life of the product; not providing stability data
6 for the predicate product; not providing water
7 activity, tobacco-specific nitrosamine levels, or
8 microbial counts.

9 It would facilitate our review to
10 provide the following types of information for
11 each tobacco product: stability data over the
12 entire shelf life of the product with at least
13 three time points such as the beginning, middle,
14 and end; the pH, water activity, and TSNA levels
15 of the products; identifying whether any
16 preservatives or microbial metabolic inhibitors
17 are used; total aerobic microbial counts and
18 total yeast and mold counts; an explanation of
19 how the storage time or shelf life is determined;
20 an explanation of any differences in the testing
21 procedures or methods used for the new and
22 predicate products. We also suggest you consider

1 testing under the storage conditions in which the
2 product is intended to be stored.

3 And now I will turn the presentation
4 over to Dr. Cecil.

5 DR. CECIL: Thank you, Dr. Rogers.
6 Good morning. I'm Todd Cecil and I'm the
7 Associate Director of the Division of Product
8 Standards in the Office of Science. I will carry
9 on the discussion of common deficiencies in SE
10 applications.

11 In addition to the chemical and
12 microbiological deficiencies discussed by Dr.
13 Rogers, there are common deficiencies in design
14 parameters provided in SE reports. The design
15 parameters directly affect the HPHC content of
16 cigarette smoke, the solvation of nicotine in
17 smokeless products, the particulate size in
18 combusted tobacco products, and aerosol droplet
19 size in ENDS and non-combusted tobacco products.

20 Design parameters may also change the
21 HPHC mixture that a user is exposed to, and
22 therefore plays an important role in

1 considerations of the effects of the change on
2 public health.

3 The first of the common deficiencies
4 has to do with missing design parameter
5 information. And as I said before, design
6 parameters are foundational information that
7 allows FDA to better understand tobacco products
8 and fully characterize the new and predicate
9 tobacco products.

10 Comprehensive design parameter
11 information for both new and predicate tobacco
12 products is important in making an SE
13 determination. The FDA has encountered SE
14 reports that lack comprehensive data parameter
15 information, including and specifically the
16 target values for individual design parameters
17 and the range limits for those design parameters.

18 Now we recognize that design
19 parameters may exist in your facilities in
20 something that you term a manufacturing data
21 sheet --- or at least you've heard it called, I
22 think the nomenclature discussion yesterday was a

1 good point made --- and it may facilitate FDA's
2 review if you were to include these documents
3 with your application. If you are to include
4 manufacturing data sheets and those data sheets
5 reference certificates of analysis or standard
6 operating procedures, it would further facilitate
7 our review if you were to provide those to us as
8 an appendix to your data sheets.

9 It would also facilitate our review to
10 provide target specifications and upper and lower
11 limits to the following types of design
12 parameters for each new and predicate tobacco
13 product: the product dimensions, length, width,
14 diameter and so forth; product mass and tobacco
15 mass, if appropriate, tobacco moisture content
16 if, again, appropriate; tobacco cut size and then
17 particle size; characteristics of all the papers
18 that are being used, cigarette paper, tipping
19 paper, filter wrap, and pouch paper for smokeless
20 portioned products; filter ventilation, and
21 characteristics of the filter if it's a filter
22 product.

1 While the design parameters differ by
2 the type of tobacco product you're working with,
3 this list is generally applicable, and a better
4 list is included in the acknowledgment letter
5 that was discussed yesterday and will be on the
6 website at some point.

7 Along with missing design parameter
8 information, we've had issues with certificates
9 of analysis from material suppliers. These
10 certificates of analysis may be used to provide
11 information on the design parameters, and they
12 have been provided to us in the past. However,
13 we have found that often they are missing
14 components. So it would facilitate FDA's review
15 if you were to ensure that any COAs received
16 include target specifications, quantitative
17 acceptance criteria, or tolerances, units of the
18 parameters, the test data average value, and
19 minimum/maximum values for test data. And I'll
20 speak on test data in a few moments. If a
21 certificate of analysis is supplied, we would
22 request that those certificates of analysis be

1 complete and unaltered COAs from the
2 manufacturing supplier.

3 In addition to issues with missing
4 parameter information, there have also been
5 issues with missing test data. The FDA will
6 occasionally need the test data to confirm that
7 specifications are met. Test data are measured
8 values of design parameters, and they are a
9 critical parameter of importance because the data
10 indicates whether the product that you have
11 tested can reproducibly be provided to ---
12 manufactured in that manner over extended periods
13 of time. So a COA from a manufacturing supplier
14 may provide inadequate information and parameter
15 tested data.

16 The FDA has encountered SE reports
17 that provide COAs, but that did not include all
18 the data needed to assess that parameter,
19 specifically test data and averages, did not
20 explain how nonconforming data are handled. In
21 many cases we have seen that the COAs provided
22 extend beyond the acceptance ranges of the

1 parameter that have been stated for that design
2 parameter. If the test data do fall outside the
3 range limits, it would be helpful if you would
4 supply an explanation as to how the nonconforming
5 data is handled and why the nonconforming data
6 does not raise different questions of public
7 health.

8 Test data are especially important in
9 cases where there is a difference in the target
10 specification between the new and the predicate
11 products. The range limits of the tobacco
12 products in other cases, the range limits of the
13 new tobacco products are wider than those of the
14 predicate tobacco product.

15 It would facilitate FDA review if the
16 test data for each parameter provides the
17 following for each new and predicate tobacco
18 product. Test protocols, quantitative acceptance
19 criteria, the data sets themselves, the summary
20 of the results of the new and predicate tobacco
21 products, and data lists on a per unit of measure
22 of the product basis. Again, hopefully with the

1 same units of measure for new and predicate.

2 Another form of common deficiencies we
3 find has to do with interchangeable materials.

4 If you manufacture a new and predicate product
5 that may be constructed using different
6 interchangeable materials, then each unique
7 combination of those materials is considered to
8 be a unique tobacco product, and therefore would
9 require a unique submission.

10 So if there are differences between
11 the interchangeable materials that you have
12 identified in terms of ingredients, additives, or
13 design parameters, that constitutes a new tobacco
14 product. However, a distinct new tobacco product
15 may use the same predicate product for
16 comparisons.

17 FDA has encountered SE reports that
18 provide unclear descriptions of what information
19 applies to which product submitted in the SE
20 report. Often there's a listing of all of the
21 options in a single table and it's unclear which
22 is being used at any given time.

1 It would facilitate FDA review to
2 provide the following information for each
3 tobacco product: every unique material
4 combination, each specific combination of
5 materials will be considered a new tobacco
6 product and be evaluated individually; a list of
7 ingredients and ingredient quantities for each
8 identified material for each product; target
9 specifications and upper and lower range limits
10 for all the design parameters for each material
11 and each product; test data including test
12 protocols and the methods in which you tested the
13 materials; quantitative acceptance criteria, data
14 sets, and the summary of results as we spoke to
15 previously, for all the design parameters for
16 each material and each product.

17 If an interchangeable material is
18 used, options include identifying a single unique
19 new tobacco product and a single unique predicate
20 tobacco product with a defined set of
21 interchangeable material. With this option, the
22 interchangeable material will not be reviewed,

1 and the SE determination will be made only on the
2 specified new product identified. Every new
3 unique predicate -- new and predicate tobacco
4 product that may result from an integration of
5 each of the combinations and all the permutations
6 of those ingredients may also be provided. The
7 SE report would need to have a distinct
8 comparison of the new and the predicate product
9 for each of those permutations.

10 The third option is to follow a
11 bracketing sort of approach to demonstrate that
12 the interchangeable materials do not cause the
13 new tobacco product to raise different questions
14 of public health. And an example of how that may
15 work is to compare unique versions of both the
16 new and the predicate tobacco product that
17 generate the highest yields of HPHCs with the
18 unique versions of the new and predicate product
19 that provide the lowest yields of HPHCs.

20 Another common deficiency has to do
21 with dissolution testing and it is specific to
22 smokeless products. So in cases where new and

1 predicate smokeless products have differing
2 design parameters or chemistry changes such as: a
3 pH additive; a target pH change; addition or
4 changing of the binders and the fillers in the
5 tobacco blend; tobacco particulate size has
6 changed, or the pouch materials are different
7 between the new and predicate products.

8 These changes may result in associated
9 changes in nicotine release and in total nicotine
10 release. And the changes in nicotine release can
11 affect user perception and user initiation and
12 use patterns, and thus affect the public health.
13 So nicotine release information could be obtained
14 and provided through a series of release studies
15 in simulated saliva using an in vitro dissolution
16 experiment.

17 The FDA has received these dissolution
18 testing results and has encountered reports that
19 lack information including: the dissolution
20 apparatus, are you using the paddle and basket or
21 are you using Apparatus 4; dissolution
22 conditions, the media, the temperature, the stir

1 rate or the flow rates, depending upon the type
2 of apparatus used; the dissolution media, what
3 pH, what buffers, are you using enzymes, are you
4 de-gassing the medium, which may be important for
5 tobacco products.

6 A description and rationale for the
7 sampling time points -- early time points are
8 preferred, but rationale as to why the time
9 points were selected; description of the sample
10 size and disposition, how was it added to the
11 vessel? How is it maintained in a single
12 location? Are there sinkers used? Do you use
13 mesh? There's other ways of containing the
14 materials.

15 The percentage of nicotine release
16 relative to the T-infinity point of the time
17 versus -- or sample versus time plot.
18 Occasionally we receive dissolution criteria that
19 show total release, but does not compare to
20 percent at the T-infinity time point, which does
21 not provide an understanding or ability to
22 normalize between individual ones. For those who

1 aren't aware, T-infinity is determined by
2 increasing the flow rate for a period of time
3 until you reach a steady state and a maximum
4 released in that period of time.

5 And finally, full analytical testing
6 information should be provided, as Dr. Rogers
7 talked about previously. It's often called the
8 analytical finish.

9 Now I'd like to move on to talk about
10 common deficiencies in HPHC analysis,
11 specifically in modeled systems, and the
12 toxicological evaluation of changes in HPHCs.
13 FDA has received SE reports where some data were
14 based on modeling of the design characteristics
15 of the new or predicate tobacco products, but the
16 SE reports did not provide sufficient evidence to
17 demonstrate the accuracy of the model being used.

18 So these SEs that we've encountered
19 lacked critical design characteristics used in
20 the model or a description of those, a
21 description of the variables that the model was
22 designed to predict, the assumptions and

1 rationale for excluding a variable, the
2 acceptable prediction error for each modeled
3 variable.

4 The test set that was actually used,
5 including the prediction and the measured values,
6 this is often termed the validation of your
7 predictive model. And a calculation of the
8 prediction error, confidence interval, and the
9 prediction interval for each modeled variable.
10 This information provides a better understanding
11 for the use of that modeled information and the
12 confidence that can be assigned to the data
13 produced.

14 Now shifting gears, talking about
15 toxicity and the toxicological evaluations. When
16 addressing the potential effects of product
17 changes --- and here product changes are, I'm
18 including product design, chemical differences,
19 microbiological changes --- it's helpful for the
20 manufacturer to account for specific changes in
21 ingredients. Where the ingredient is -- again,
22 Dr. Rogers talked about this previously in her

1 slide. We need to consider the route of exposure
2 and the effects of the changes upon HPHC
3 delivery. We need to specifically also consider
4 the ingredient itself if it were to sublime
5 into the vapor phase of a cigarette or be
6 released in a smokeless product. And the effects
7 of the degradation of that through combustion or
8 through other interactions that may occur in that
9 material as it's released to the user.

10 Some of the approaches to address
11 toxicity of a product change can include
12 submitting data showing there are no increases in
13 the HPHC delivery. The second option is to
14 provide in vitro studies to address the human
15 cancer risk and non-cancer hazards due to the
16 HPHC increases. It would facilitate our review
17 to include a rationale for how the studies
18 address the expected human risk and non-cancer
19 hazards. Each study may potentially address
20 concerns about human health effects of
21 ingredients in their unchanged form.

22 A third approach is to provide

1 toxicological analyses of ingredients or HPHCs
2 that have been or can be used to establish health
3 protective reference values applicable to
4 anticipated human exposures of use for the new
5 tobacco product, and how the reference values
6 address the toxicological effects expected from
7 the new tobacco product ingredients or HPHCs.

8 Note that the reference values based
9 on non-cancer endpoints do not support
10 carcinogenic HPHCs. In the absence of compelling
11 data supporting the dose threshold below which
12 carcinogenicity of a compound definitely does not
13 occur, it is toxicological practice to assume a
14 linear relationship between dose of the
15 carcinogen and increased risk of cancer.

16 An ingredient's status as a generally
17 recognized as safe material has not been
18 evaluated for inhalation exposure. The FEMA
19 website is perfectly clear that GRAS is not
20 intended for inhaled products. And the GRAS
21 status is dose dependent and that would need to
22 be considered in your application.

1 In these toxicity analyses, it is
2 important to consider the following parameters:
3 the route of administration; the relevance of the
4 animal species tested including the strain and
5 sex-specific effects; dose response profile;
6 exposure and frequency of duration -- frequency
7 and duration, sorry; adverse and critical effects
8 identifiers such as the LOAEL; adjustment of the
9 critical effects level of dose metrics of
10 interest; biological significance of the response
11 that is being followed; interpretation of results
12 and relevance of uncertain factors used --
13 uncertainty factors, pardon. Availability of
14 supporting evidence and relevance and results in
15 human; and finally, the available information on
16 the metabolic fate and disposition of the
17 ingredients.

18 Another approach might be to provide
19 a quantitative risk analysis. HPHC comparisons
20 are an important aspect of a toxicity evaluation
21 for new and predicate products in SE reports.
22 It's important to note whether the HPHC increases

1 have an offsetting HPHC decrease. A quantitative
2 risk analysis approach may only be useful in
3 addressing HPHC increases in specific situations
4 where both HPHC increases and decreases are
5 found. QRAs by themselves cannot address HPHC
6 increases and are not useful if there are no HPHC
7 decreases that could possibly offset an HPHC
8 increase. If there are only HPHC decreases and
9 no HPHC increases, there's no reason to go
10 through a QRA.

11 HPHC measurements used that are not
12 statistically and analytically different from the
13 predicate product values may not provide
14 information to help in the QRA. To be a little
15 more precise, cases where you're within the error
16 of the analytical technology, if the change is
17 one or two percent and the error in your method
18 is five or ten percent, those data may not be
19 statistically different.

20 So prior to looking at a quantitative
21 risk analysis, it may be in your best interest to
22 consider a qualitative analysis before embarking

1 upon an expensive and comprehensive quantitative
2 approach. Such an analysis can help determine
3 whether a quantitative approach would be useful
4 or unnecessary. And again, it's critical that
5 the qualitative analysis focus on only the
6 statistically and analytically different HPHC
7 measurements.

8 If a QRA is submitted, it would
9 facilitate FDA's review to include the following
10 information: the specific questions addressed by
11 the QRA and clearly defined -- a clear definition
12 of the overall risk model; a well-developed and
13 scientifically supported risk assessment
14 including problem formulation, hazard
15 identification, dose response assessment,
16 exposure assessment and risk characterization as
17 outlined by the NRC of the National Academies.

18 All raw data equations, assumptions,
19 parameters, outputs and references used, it would
20 be beneficial if that information was included as
21 appendices and referenced, rather than included
22 in the body of the QRA. Justification that the

1 QRA is appropriate for comparing the relative
2 human health risks and hazards from use of new
3 and predicate tobacco products for the relevant
4 user population.

5 All relevant measured HPHCs or other
6 constituents of potential toxicological concern
7 employing, as much as possible, a consistent risk
8 assessment approach for all constituents being
9 evaluated. Evidence that the constituents
10 considered in the composite QRA are
11 representative of potential differences in the
12 cumulative hazard and risk of the tobacco
13 products. And finally, the evidence that the
14 evaluation can discern a difference in hazard and
15 risk between the new and predicate tobacco
16 products.

17 In summary, this presentation of both
18 Dr. Rogers and myself has covered a wide array of
19 topics and only covers the most general and
20 often-encountered deficiencies that we have seen
21 in the SE pathway. We have covered predicate
22 tobacco product issues, ingredient issues,

1 constituent reporting issues, product design,
2 HPHC, and toxicological analysis. And with that,
3 I'd like to say thank you very much for your time
4 and attention.

5 MS. JOHNSON: Thank you so much to our
6 FDA SMEs. And now we would like to invite our
7 panelists up front for the panel discussion.
8 Please don't forget that if you have any
9 questions for this panel, there will be 5x8 cards
10 passed around. You just need to raise your hand
11 and one will be given to you. This might be
12 lively. I hear a lot of chitter chatter.

13 MR. BUELL: That means we've got lots
14 of questions.

15 MS. JOHNSON: That's good. That will
16 keep it lively. Okay, are we all set? Okay.
17 Okay, we want to get started so we can try to
18 stay on time today. Each one of our guest
19 panelists will have five minutes to introduce
20 themselves and make statements or comments on the
21 presentations that were just presented to us. We
22 will start with Robert.

1 MR. BUELL: Good morning. My name is
2 Rob Buell. I'm with Altria in the Regulatory
3 Affairs Department. And for the last few years,
4 I've led a team of people responsible for SE
5 submissions for our tobacco companies.

6 First, I would like to thank FDA for
7 hosting this important forum, and for the
8 opportunity to share with you this morning,
9 Altria's perspective and experience with the SE
10 pathway.

11 In announcing this meeting,
12 Commissioner Gottlieb stated that we all need to
13 be on the same page regarding the basic rules of
14 the road, especially when it comes to what's
15 expected in pre-market applications. We could
16 not agree more. Those words were true in 2011
17 when the first SE reports for provisional
18 products were due, and they're even more true
19 today as we have been operating over the past
20 eight years without the benefit of these critical
21 foundational rules.

22 Until such rules are in place, we are

1 concerned that the SE process will continue to be
2 characterized by uncertainty, by lack of
3 transparency, and by ever-evolving requirements
4 that have been applied inconsistently over time
5 across reviewers and often from one application
6 to the next. That is why we continue to advocate
7 that the most significant step that FDA can take
8 to improve the SE pathway is to issue, through
9 notice and comment rule making, binding
10 regulations that interpret and apply the pathway
11 as Congress intended.

12 And most critical in that regard, FDA
13 needs to issue a rule that clarifies its
14 interpretation of the key statutory terms that
15 govern substantial equivalence. Among those
16 being same characteristics, different
17 characteristics, and different questions in
18 public health. And FDA must articulate the
19 standards that it is applying in practice to make
20 these SE determinations.

21 As we've heard over the past two days,
22 Congress created two separate and independent

1 prongs or tests for substantial equivalence. The
2 first question asks, do the predicate product and
3 the new product have the same characteristics?
4 If the answer to that question is yes, the new
5 product is substantially equivalent and the
6 inquiry should stop there. If and only if the
7 new and predicate product have material
8 differences in their characteristics, differences
9 that have the potential to raise an issue in
10 public health, do you proceed to the next step,
11 which is does the new product in fact raise
12 different questions of public health.

13 Now that second question we submit is
14 a much broader one than the first. It is not
15 limited to a side-by-side comparison against a
16 single predicate product. Rather, different
17 questions of public health must be measured
18 against those risks already posed by products
19 that Congress grandfathered and allowed to remain
20 in the marketplace without FDA approval. So if a
21 new product raises risks to public health that
22 are no different than those presented by the

1 marketplace of legally marketed tobacco products
2 in that same category, then it should be found
3 substantially equivalent under the second prong.

4 Now it has been our experience however
5 that FDA has conflated these two separate and
6 independent prongs into a single test that it
7 applies to all submissions. First, FDA appears
8 to be interpreting same characteristics so
9 restrictively that any difference between the new
10 and predicate product, no matter how small or
11 insignificant from a public health standpoint,
12 pushes the application into the second prong for
13 the different questions of public health
14 analysis. And that effectively writes out of the
15 statute the first prong for same characteristics.
16 It never gets applied.

17 Then FDA looks at the differences in
18 isolation to determine whether each one
19 independently raises a different question of
20 public health. Again, by doing that, it's
21 comparing only to the predicate product, which
22 ignores the basic -- or the baseline public

1 health risks that are already inherent in the
2 marketplace from grandfathered products. By
3 using the very, very broad term public health in
4 the second prong of the SE test, Congress was
5 indicating that it did not intend for that prong
6 to be constrained by the characteristics of a
7 single predicate product.

8 I say this appears to be what FDA is
9 doing in applying the SE test. It's unclear
10 because as I stated, we don't have the
11 foundational rules in place that Commissioner
12 Gottlieb has spoken of. And it's our hope that
13 with the proposed rule that is now pending at the
14 Office of Management and Budget, that we will
15 finally get some badly needed clarity and
16 transparency on these issues that I've addressed.

17 Thank you very much for your time this
18 morning. I look forward to the rest of the
19 conversation.

20 MS. JOHNSON: Thank you so much. Tom?

21 MR. LINDEGAARD: Well Rob, I can only
22 say you took the words right out of my mouth. It

1 must have been while --- no. But good morning,
2 everyone. My name is Thomas Lindegaard. And
3 despite my appearance on the panel yesterday, I'm
4 still senior vice-president of the Scandinavian
5 Tobacco Group dealing with scientific and
6 regulatory affairs. I'll repeat a few things. I
7 have 25 years of experience working within this
8 industry on scientific and regulatory matters in
9 product development. And I've been deeply
10 involved in the submissions of SE on behalf of
11 our company. Just like yesterday, I'd also like
12 to raise a few points which hopefully can inspire
13 the questions and discussion.

14 The 25 years in the industry, I was
15 also around at the time when the issue of
16 additives to tobacco became interesting for
17 regulators and the public in general. We made
18 the mistake of assuming at that time, that it was
19 a technical scientific issue. But the reaction
20 we received from many politicians, from the
21 public in general was certainly much more of an
22 emotional one. But I would however expect that

1 anyone here today; Dr. Holman, Dr. Cecil, Rogers,
2 et cetera would agree with me that it is
3 rightfully a scientific issue and should be dealt
4 with in this way.

5 And my question here today is when we
6 look at the SE process as it's being managed, is
7 it really treated as a scientific issue all the
8 way through? I would like that to be part of the
9 discussion. I'll go into a little bit more
10 detail. Everyone here knows for sure that it is
11 impossible to quantify the differences in risk
12 between a predicate and a modified product.
13 They're almost, well by definition, almost
14 identical. And even if they were put to the
15 ultimate test of epidemiological studies through
16 40 years, we would most certainly not see a
17 difference in the relative risk. We know for
18 sure that products with much bigger differences
19 than what we see in these analyses, they do not
20 come out different.

21 Now the SE process as we see it is not
22 concerned with documenting relative risk. I

1 think it should be, but it's not. It's about, as
2 Rob mentioned, looking for new questions of
3 public health. That's what's happening. And new
4 questions of public health is not very well
5 defined. To me, it's not defined in the laws of
6 whatever interpretation exists. I must assume it
7 comes from FDA or the Office of Science.

8 And when I look at how this is
9 interpreted, it's not only very strict, but in my
10 view also not fully supported by science. When
11 we have a product where one of the modifications
12 was a change in the glycerine content from 0.21
13 percent to 0.36 percent and we had to document
14 that there were no new questions of public
15 health, well I thought this was going to be easy
16 because there are so many excellent studies out
17 there; peer reviewed including all the elements
18 that we saw described just a minute ago that
19 demonstrate very clearly that you can use up to 5
20 percent glycerine in a tobacco product without
21 any adverse effects.

22 We submitted these peer reviewed

1 studies feeling very confident, only to get the
2 answer back. No, that was not good enough. It
3 wasn't tested on your blend in the lower
4 concentrations. And I mean, that just
5 illustrates to me that you can keep on asking
6 these type of questions. There is no end to
7 these type of questions, especially if you
8 disregard the science that is already out there.
9 And the problem with using empirical science is
10 that you can never prove anything to be 100
11 percent true. You can always ask new questions.

12 So my question, a new question here
13 today is what is this definition of new questions
14 to public health? My claim is based on our
15 experience that it is not being -- it is not
16 scientifically solid, but please prove me wrong.

17 My only other point is that if this
18 level of scientific scrutiny is applied to the
19 deemed products, it will lead to a chaotic
20 situation. The number of SKUs is astronomical.
21 The volumes are minute on these brands. The
22 products are typically produced by hand in a

1 very, very low tech setup.

2 As I mentioned yesterday, the basic
3 quality control equipment is a ruler and a scale.
4 I mean and the quality control is based on
5 stuffing a pipe and lighting it up, smoking it or
6 lighting up a cigar, tasting it. The most basic
7 information about HPHC states it does not exist
8 and certainly not for products, which are 11
9 years old. So what are the new questions with
10 public health and please don't apply this one
11 size fits all approach to the deemed products as
12 well.

13 MS. JOHNSON: Thank you. Mark, your
14 comments please.

15 MR. SCHEINESON: Yes. Good morning.
16 Yes, thank you for the honor to participate on
17 this panel today. I'm the guy in the trenches
18 that has to prepare these reports. I'm Mark
19 Scheineson. I have the Food and Drug Practice at
20 the Washington DC office of the law firm Alston &
21 Bird. I'm a former FDA associate commissioner
22 for legislative affairs where I had the honor of

1 serving FDA commissioner, Dr. David Kessler in
2 the early 90s and HHS secretary, Louis Sullivan.

3 I practiced FDA law for over 30 years,
4 primarily in the drug and medical device field.

5 My practice has included participation in
6 drafting and implementation of the Tobacco
7 Control Act on behalf of a variety of small
8 tobacco product manufacturers and associations.

9 While representing those clients, I participated
10 in the drafting of many dozen substantial
11 equivalence reports for cigarettes and smokeless
12 products and preparing responses to the various
13 rounds of FDA follow-up correspondence.

14 Based on this experience, my
15 colleagues and I have the following suggestions
16 to clarify and improve the existing SE reporting
17 process. The first is to recognize that the
18 intent of the Tobacco Control Act was to regulate
19 tobacco products, not to eliminate them. Use the
20 tools granted by Congress as they were intended,
21 including greater use of exemption requests for
22 minor modifications, which Commander Walters

1 excellently described. Initially FDA viewed
2 minor modifications for this exemption process
3 very narrowly as only traditional tobacco
4 additives. Now additives are being reviewed more
5 broadly as applying for example to fire safe
6 cigarette paper, which will eliminate thousands
7 of potential applications.

8 Support the legislative change of the
9 predicate date. You've all heard this debate.
10 The February 15, 2007 date was never intended to
11 remain in the final Tobacco Control Act
12 legislation. I was there at the time. It was a
13 placeholder. It was the date of the introduction
14 of the first Senate version of the bill to freeze
15 industry conduct, so grandfathering under the act
16 could not be manipulated while the legislation
17 was being debated. The date was problematic then
18 and it's even more problematic now, 11 years
19 later. It locks in old obsolete technology in
20 the most dangerous products. It floods the
21 agency with applications that it can't hope to
22 review timely.

1 A two year look back or look back to
2 perhaps August 8, 2014 for deemed products allows
3 FDA to evaluate most of these new technologies
4 including ENDS in a matter that's
5 administratively feasible to FDA and the
6 regulated industry. It allows ENDS products to
7 use the SE pathway and not the PMTA pathway,
8 which can solve a variety of problems as well.

9 Next, substantial equivalence does not
10 mean identical. You know, learn from the
11 accumulated experience CTP has amassed in
12 thousands of SE report reviews. For example,
13 don't expect each applicant to individually prove
14 the safety of the same cement chemicals used
15 across the industry, but recognize industry
16 standards or findings made previously by the
17 Office of Science. Use device understanding of
18 the meaning of the SE term. Similar material,
19 similar technology, performance and conditions of
20 use.

21 Consider multiple predicates if
22 individual construction of components -- or sorry

1 -- if identical construction of components is
2 required. Allow a hybrid application with
3 multiple predicates. Use rule making more, or at
4 least Class I guidance with sufficient
5 opportunity for public input. Like this, CTP has
6 enough scientific experience now to create a
7 refined checklist of the format and information
8 required in a complete SE or PMTA report. Those
9 checklists should be made available to the public
10 in the same manner as compliance policy guidance
11 or FDA's manual of policies and procedures. CTP
12 has acknowledged an intent to release technical
13 appendices addressing some of these common
14 issues, which will be very helpful.

15 Communicate decisions timely that have
16 general application. FDA CTP is confronting the
17 same or similar issues with respect to SE reports
18 continuously. It's essential that the agency
19 communicate its decisions that have general
20 application immediately through guidance,
21 addendums or otherwise.

22 Conduct basic research and allow a

1 right to reference. The agency should use a
2 portion of its vast industry user fee revenue to
3 conduct the basic research for meta-analysis
4 required for each individual applicant. You
5 know, whether it's ENDS -- whether ENDS are
6 appropriate for the protection of public health
7 because they reduce combustible product use, a
8 threshold question, or you know, the levels of
9 increased TNCOs that are acceptable in FSC paper
10 use.

11 Applicants should be permitted to
12 reference that research, rather than recreate it.
13 Just two more points. Two more points, I
14 promise.

15 MS. JOHNSON: Thirty seconds.

16 MR. SCHEINESON: The NSE process is
17 currently unfair and it's inconsistent. NSE
18 determinations are flowing more quickly with
19 fewer or no rounds of review based on internal,
20 nontransparent CTP experience, not the experience
21 of the applicant. For example, tobacco blends
22 that increase TNCOs. Other provisional

1 applications were removed from review. But they
2 contain less or no testing information in
3 products deemed to be NSE following scientific
4 review.

5 One last point. Regulations should
6 define essential terms as was discussed here.
7 The SE and the PMTA report regulation should
8 contain the specific scientific and testing
9 criteria required. And also define essential
10 terms like raising different questions of public
11 health and appropriate to the protection of
12 public health.

13 Thank you for the opportunity to
14 participate in this distinguished panel. And I
15 look forward to questions.

16 MS. JOHNSON: Thank you so much. We
17 have our FDA colleagues. Do you want to
18 introduce yourselves and then take on any
19 comments --

20 MR. HOLMAN: I guess that's a no.
21 They didn't phone a friend, but a friend showed
22 up anyways.

1 So a lot of good useful feedback. I
2 can't respond to all of it because you guys
3 really packed it in and used your time to get as
4 much in as you could. And for one of you, stole
5 a little extra time. But I will try to respond
6 and certainly my colleagues can chime in as they
7 see fit. But I'll try to respond to at least a
8 few remarks that you all made.

9 And part of the reason I jumped up
10 here is because I want to also clarify what the
11 scope of this meeting is. A lot of the comments
12 you guys made are really deep seated legal policy
13 issues that we're not here to discuss today. I'm
14 so happy to hear it. Happy to take those back to
15 the shop. But not prepared to respond to some
16 legal issues and deep policies such as
17 grandfather date. That's not the intent of this
18 meeting. The intent is to really share
19 information about what should be provided in an
20 application to us. Specific in this panel, SE
21 and EX.

22 We wanted to have this dialogue

1 because we think it's important to provide as
2 much information to you guys as to what needs to
3 be in the application. It benefits us if we get
4 a complete application and we can just evaluate
5 and decide whether we think a marketing order
6 should be issued or not. It doesn't benefit us
7 to have to go back and forth with the applicant
8 to obtain additional information. So that's why
9 we're here is to hopefully give you enough
10 information or better information, more
11 information so that you can provide complete or
12 more complete applications. So that we can have
13 fewer rounds of review. We can get to an order
14 more expeditiously, which benefits us and it
15 benefits the applicant. So that is the scope of
16 what we're here to discuss. And we're happy to
17 have conversation on that.

18 So there were a couple points that I
19 want to respond to. And again, feel free to
20 respond to some of the other points. We have
21 been hearing loud and clear that folks want us to
22 define same characteristics versus different

1 characteristics and what different questions of
2 public health mean. The way I've responded up
3 until now -- and I'll provide the same response
4 this morning, which is we try to start to define
5 same characteristics.

6 And I'm sure you all are aware that a
7 couple of years ago the courts told us that the
8 way we were trying to define it, did not align
9 with the statute the way it should. So we're
10 being very careful and trying to go forward and
11 define same characteristics going forward in a
12 way that we think the courts will support. We're
13 not there yet. We hear you. We know it's
14 certainly top of mind for you. It's top of mind
15 for us.

16 I will say one of the things we have
17 done though is started to, I think better
18 communicate the point that -- you know, the
19 volume of information needed in an SE report
20 today is really proportional to the differences
21 between the new and predicate product. I think
22 in some of the earlier SE reports, because we

1 were inexperienced, we asked for a long list of
2 characteristics and evidence and data to support
3 those differences in the characteristics between
4 the new and predicate.

5 I think one of the ways that our
6 program has evolved in a very positive way is
7 that we've gotten much better at understanding
8 significant or insignificant differences. There
9 are stark differences of opinion. Thomas is
10 shaking his head no on that comment. I agree
11 there are differences of opinion. We'll have to
12 agree to disagree on some of this stuff for sure.
13 But again, we are trying to scale the information
14 that's necessary, depending on the extent of the
15 difference between the new and the predicate in a
16 way that's reasonable. And can help us achieve
17 our public health mission while being more
18 transparent, you know, with the applicants about
19 what is needed.

20 Along those lines, I guess one other
21 point is that I think -- you know, Thomas brought
22 up the point of providing peer reviewed

1 literature and that wasn't adequate. And I can't
2 speak to his specific SE report -- the SE report
3 he's talking about. But I'll make a general
4 remark that published literature has been used
5 successfully for SE reports to get to an SE
6 order. The issue that we continue to run into in
7 terms of you know, again I'd put on a big common
8 issue or common deficiency we have is often times
9 it's not clear how that data can be extrapolated
10 to particular new and predicate product. And so
11 a lot of times, we're just looking for some sort
12 of explanation because it may not be obvious to
13 us how to extrapolate.

14 The other issue we've run into quite
15 frankly is that, you know, our evaluation of some
16 of that published literature is that it has
17 limitations. And sometimes we view the
18 limitations such that it doesn't support
19 demonstration between the new and predicate
20 product don't raise different questions of public
21 health. So again, one thing I'd just put out to
22 applicants is, you know, always explain how that

1 extrapolation, you know, works. And also explain
2 how in spite of the limitations, you feel like
3 the conclusion of those studies are supportive of
4 your SE report.

5 I will also say that Thomas raised the
6 point that, you know, deemed products and I think
7 specifically cigar manufacturers are going to
8 have challenges dealing with submission of SE
9 reports. I'm certain they will, just as the
10 statutory product manufacturers had to make some
11 adjustments to how they did business, my
12 expectation is that cigar manufacturers will have
13 to do the same.

14 That being said, we are aware -- you
15 know, we are cognizant of the situation that
16 deemed product manufacturers in. And again,
17 we're trying to provide more information, more
18 clarity. That's still a work in progress. And
19 we'll continue towards that front so that very
20 clear expectations are laid out for those deemed
21 product manufacturers as they start to -- as
22 they're beginning to put together their marketing

1 applications.

2 And then lastly, I'll respond to
3 Mark's comment about the statute wasn't meant to
4 eliminate tobacco products. We certainly agree.
5 And I think we have hundreds now of SE orders
6 that demonstrate we agree the intent of the SE
7 program is not to eliminate products in the
8 marketplace.

9 You also suggested that we do research
10 to help out manufacturers. We do do a lot of
11 research. In fact, many of our research products
12 are driven by issues that we see -- common issues
13 that we see in the marketing applications. As we
14 start to see the same issues over and over again,
15 we actually go out and do studies to say is that
16 really meaningful or not. And then we use that
17 data.

18 So once we've conducted a study and we
19 have the results, as we continue to see those
20 issues, we now know whether in fact that is a
21 concern or not. And so there are a number of
22 issues where maybe in the early SE reports at the

1 beginning of the program, we would raise a
2 deficiency about certain differences in
3 characteristics. Then we went out and did some
4 studies. And then now we've been able to say oh
5 actually, that isn't a concern for us. We don't
6 think that difference raises a different question
7 on public health. Again, based on data that we
8 were able to collect to give us certainty about
9 what that difference means.

10 So with that, I'll turn it over to my
11 colleagues if they want to add anything else.

12 MR. SCHEINESON: If not, we have more
13 questions.

14 MS. ROGERS: Okay, how's that for
15 clarification? Just one comment that I don't
16 think was addressed by Dr. Holman that seemed to
17 be a theme for all of you. And that's the need
18 for rules -- published rules. And we at FDA
19 share your frustration with the slow process --
20 of the rule making process. And in the absence
21 of those rules, we are trying to be more
22 transparent through things like this meeting here

1 today, the new notification letters that were
2 described yesterday, and other means.

3 MR. SCHEINESON: Just two comments and
4 thank you. I don't want to cut you off. And
5 it's very nice to get this feedback. This is
6 very helpful. Your overheads are very helpful.
7 It is a bit of a wish list and you know, Dr.
8 Rogers, when you highlighted, you know, a lot of
9 information that for small businesses doesn't
10 exist and doesn't exist in their product
11 manufacturers, this just isn't the way that the
12 COAs were constructed. It's a new paradigm
13 that's here. It may improve products. It's
14 certainly going to make them more consistent.

15 When you said this would help our
16 review, are those maybes or musts? Are those
17 requirements or it would be useful to have that
18 information, but it's not required?

19 MS. ROGERS: Well in the absence of
20 the regulation, it's not required --

21 MR. SCHEINESON: Right.

22 MS. ROGERS: -- but it is very helpful

1 for our review. And we do request that
2 information.

3 MR. SCHEINESON: And the other concern
4 that I hear most -- and thank you for sharing
5 this feedback is a number of these items, you
6 know, whether it's stability or testing to
7 specifications, those are GMP requirements.
8 Those aren't really what was envisioned in
9 determining whether a product is substantially
10 equivalent to another product; shelf life and
11 validations. And those are all -- you know, we
12 know those from drugs and devices. I mean I've
13 spent my career on those. They are very
14 complicated, very expensive concepts. But
15 they're GMP concepts. And you know, the law
16 envisions some GMP regulations. Everybody's
17 being inspected, but not to GMP regulations that
18 exist.

19 How can we work together to prioritize
20 and to maybe push some of those into boxes that
21 would be GMP and equally valid and could be
22 substantiated, but really wouldn't hold up an SE

1 report?

2 MR. CECIL: I can speak to the
3 validation specifically. The validation is not a
4 GMP concept. Validation is something that
5 demonstrates that your amicable methodology is
6 capable of doing the measurements and providing
7 valid data. That is not what -- And that is the
8 definition of what validation is. So a validated
9 analytical methodology and a validated process
10 are two different animals. And I recognize that.

11 There are some things that are GMP
12 related. But again, it's important in case of
13 design parameters, that we understand what the
14 intention of that product is. And what it -- If
15 we're claiming to say that they are the same,
16 what does "the same" mean? And if there is plus
17 or minus 90 percent, that's not the same. That's
18 another -- we don't know what that product is.

19 And so I think we're not trying to say
20 you have to implement TPMPs yet. But I think
21 this is something that we do at some point need
22 to understand what the products are.

1 MR. SCHEINESON: Great.

2 MR. CECIL: We don't have that
3 experience in-house.

4 MR. LINDEGAARD: Can I have a follow-
5 up question on that? You have presented, Dr.
6 Cecil, a lot about the HPHC data, which would be
7 helpful. But again, to me it is an illustration
8 of how you focus on the extreme details and
9 forget to look at the bigger picture.

10 A few months ago, I presented some
11 data at the Tobacco Science Research Conference
12 with HPHCs in leaf from the exact same tobacco
13 grades, just from different crop years or from
14 one field to another field just next to it. And
15 the variation was just enormous. It was like the
16 90 percent you talk about. And these were
17 tobaccos that were graded out to be exactly the
18 same stock precision whatever, just coming from
19 another crop year.

20 So how do you take that into account
21 when you want to compare a predicate and a
22 modified product where there could be crop

1 changes involved of this type of magnitude?

2 We're certainly in the dark about this.

3 MR. CECIL: When dealing with
4 differences in crop year, tobacco is a blended
5 product. Tobacco products are blended. You take
6 a blend and you try to come up with a flavor that
7 is the same. You're blending tar into nicotine.
8 There's a lot of HPHCs that could be tested and
9 blended as part of that process. We don't know
10 if that's being done. All we have to work with
11 is what is provided to us in your application.

12 If you're able to show from year to
13 year to year that there is huge variability, well
14 that's fine. We need to understand what that
15 variability is and why it exists. And simply
16 saying that it is because of crop year
17 variations, that doesn't tell us what is an
18 expectation. Your users have an expectation.
19 The agency has an expectation as well as to what
20 is the consistency of this material? Especially
21 if you're making statements that this has a
22 certain public health impact. If it goes up to a

1 very high level, then we should be evaluating the
2 very highest level because that is the level at
3 which the toxicity will affect the user the most.

4 If you're saying it's an average
5 value, then we need to work with an average
6 value. We need to understand what that average
7 value is. So an understanding of that
8 variability is critical. So when you publish
9 that paper, we would be very interested in
10 looking at it and seeing if there's any way to
11 incorporate the concepts.

12 MR. SCHEINESON: Another real world
13 question. And I may not be invited back, so I
14 apologize. Feel free to punt -- you know, we're
15 all doing this for the first time and we
16 acknowledge that. And that's why this
17 interaction is so important and so meaningful.

18 From the small tobacco manufacturer
19 perspective, you know, we're getting letters back
20 that literally have 25 requests for information.
21 A lot of it requires extensive testing. That
22 testing per SKU can be \$100,000. These

1 companies, you know, don't have the money to do
2 that. You know, Altrias of the world do. The
3 small tobacco manufacturers don't.

4 A lot of these companies have fire
5 safe paper that has boosted their TNCOs. Because
6 in 2009, you know, nobody knew except the most
7 sophisticated companies that that effect could
8 occur. But there's a benefit for not burning
9 your house down. But how do you advise a company
10 that has 25, you know, requests for information
11 that are going to cost them millions of dollars
12 when they don't know whether they can even get
13 past the boost of TNCO because they don't know
14 what the percentage is that you consider raising
15 a different question of public health?

16 MS. ROGERS: Well I would recommend
17 that the applicants take a good look at which
18 products they're choosing as the predicate
19 product. You now have a good idea of the types
20 of information FDA is looking for in the SE
21 report. And you can look and see between your
22 new product and the predicate product where the

1 differences are and how large those differences
2 are. And so they may want to carefully select
3 their predicate product for comparison.

4 MR. SCHEINESON: Well a lot of these
5 companies don't own those predicates. They can't
6 get them to the extent that if they weren't made,
7 they don't have the detail that you're requiring.
8 I mean have any substantial equivalence reports
9 been approved using a surrogate or present day
10 predicate that wasn't identical?

11 MS. ROGERS: If the question is
12 whether any SE reports have been approved using a
13 product that was not identical, yes we have.

14 MR. SCHEINESON: How about a predicate
15 not owned by the manufacturer?

16 MS. ROGERS: I don't know at this
17 point. I don't have all those details off the
18 top of my head.

19 MR. SCHEINESON: There's 170 approvals
20 out of 3,000 applications. A lot of those were
21 very minor, you know menthol to non-menthol or
22 just fire safe paper or cigarette rolls and not

1 the core products, but I mean these -- you know,
2 in the real world and that's what this feedback
3 is, these are kind of the decisions that have to
4 be made. And we want to work together to try to
5 make them.

6 MS. JOHNSON: Thank you.

7 MR. CECIL: And as Dr. Walters said
8 earlier, a non-FSC to FSC switch is an exempt
9 pathway if that's the only change they made. If
10 they said well, we're making this change and
11 we're going to change the tobacco blend because
12 it's cheaper for this manufacturer and we're
13 going to change ventilation, then we don't know
14 what the effects of those changes are. And we
15 have to take a look at that.

16 MR. SCHEINESON: The trouble is
17 manufacturers and suppliers change. And you
18 can't control them going out of business or
19 staying in business. If one supplier -- And the
20 suppliers are using that leverage to blackmail
21 companies by doubling or tripling their prices
22 because they know that's like a manufacturing

1 change for a drug or something. That will, you
2 know, eliminate their ability to be substantially
3 equivalent.

4 MS. JOHNSON: So a question that we
5 have from the audience about HPHCs and deemed
6 products and manufacturers is what advice does
7 CTP have right now for deemed manufacturers who
8 have to plan for testing? Is there a tool kit in
9 the works or you know, is there a step by step 1,
10 2, 3 things that they should plan for right now?

11 MR. CECIL: Deemed is a rather broad
12 topic. ENDS is a very different animal than
13 cigarettes or pipes or little cigars. And it
14 will depend upon each of those sorts of products.
15 ENDS, the greatest concern is carbonyls. And
16 there is data in the literature that suggest that
17 carbonyls can exceed that of cigarettes. So that
18 is what we would want to make sure that there is
19 no change in carbonyls.

20 Nicotine delivery is important
21 obviously for cigars and pipes. Many of the same
22 aspects of cigarettes would be of concern. And

1 obviously all the pieces can't be that there is
2 no paperwork to look at. There's different kinds
3 of wraps and so forth that have to be dealt with.
4 So common sense is probably the best way to look
5 at it. But look at what's already out there in
6 terms of cigarettes and smokeless products.

7 MS. JOHNSON: Another question related
8 to HPHCs ask for an elaboration on the types of
9 methods for in vitro testing for HPHC toxicity.
10 What's acceptable to CTP?

11 MR. ROSENFELDT: Hi. My name is Hans
12 Rosenfeldt. I'm the deputy director of the
13 Division of Non-Clinical Science at CTP.

14 So right now, there are no regulations
15 for in vitro or in vivo testing. The key point
16 is to make sure that the end point that you're
17 looking at can actually, you know, distinguish
18 differences. That is a key point. Also,
19 remember the user. It's important that you focus
20 your analysis on the entire mixture or at least
21 address the entire mixture. Tobacco is a
22 mixture. In a lot of studies, mixtures are

1 fractionated in different ways that could affect
2 the results. So that would be one main way of
3 looking at it.

4 MS. JOHNSON: Thank you, Hans. Let's
5 see. Question from the audience. Does CTP
6 require blood and urine results from consumers to
7 establish the impact of flavors on HPHC in
8 smokeless products? And if so, what basis does
9 CTP require this?

10 MR. CECIL: We do not require blood
11 and urine samples in any way, shape or form. We
12 prefer in vitro data. We're chemists and
13 engineers. We sort of like to stay away from
14 that.

15 There are cases where it is
16 appropriate where there are cases where a
17 manufacturer wishes to demonstrate that the
18 changes do not cause differences in uptake of
19 nicotine and there are no markers of toxicity. A
20 manufacturer may choose to go there, but it is
21 not necessarily a requirement of the SE pathway.

22 MS. ROGERS: Thank you. And I'll add

1 to that, that if a manufacturer feels like they
2 want to undertake a study with humans looking at
3 things like blood and urine samples for an SE
4 report, we would recommend that they come in for
5 a pre-meeting and discuss the study design with
6 us in advance to make sure that that's
7 appropriate for what they want to look at.

8 MS. JOHNSON: That's a good point.
9 That's a good point to carry over from yesterday.
10 Question about what constitutes a different
11 question of public health? For example, what
12 amount of increase or decrease in HPHC requires
13 an explanation that it does not raise different
14 questions? When is a modification or change in
15 product considered to be different that requires
16 an explanation?

17 MR. CECIL: Well again, public health
18 is a bigger topic. If we're looking at simply
19 dealing with DPS sort of issues, which is
20 chemistry and engineering, we're looking for
21 changes in a product design and in materials that
22 may show an increase in HPHCs. That increase

1 needs to be above the analytical variability of
2 the analytical methodologies. And we take that
3 into account when we're evaluating the
4 differences between new and predicate product.
5 Obviously if they all go down, that's a great
6 sign.

7 If there is a change that's an
8 increase in HPHCs, those are referred to the
9 clinical and non-clinical branches for their
10 evaluation to determine whether or not they may
11 show an increase in potential health effects,
12 whether in toxicity or whether it has to do with
13 addiction or one of the other clinical endpoints
14 that are of concern to public health.

15 MS. JOHNSON: Thank you.

16 MR. BUELL: So may I add and ask one
17 clarifying question? So in the presentations
18 over the last couple of days, I did not see any
19 reference to what we have learned are important
20 analytical differences that are used internally
21 at FDA for evaluating HPHCs. We learned about
22 that through FOIA of an internal memo. And I was

1 wondering if you could comment on how those
2 impact your evaluation?

3 MR. CECIL: That's a long discussion.
4 The important analytical -- It's pure analytical
5 chemistry. And we're looking at the variability.
6 It all links back to the variability of the
7 analytical methodologies and the levels at which
8 we are measuring individual toxic components. So
9 obviously a product -- Well obviously for
10 chemists, a HPHC that's at a nanogram level is
11 going to have greater variability than an HPHC
12 that's at microgram levels. And therefore we
13 recognize that there's a greater variability.
14 And we allow a greater difference between those
15 products than we do for something that's a much
16 higher concentration. And so it is -- as you
17 received through FOIA, it's linked completely and
18 definitively to the variability of the analytical
19 methodologies.

20 MS. JOHNSON: Thank you. Thomas, did
21 you have anything else on it?

22 MR. LINDEGAARD: Just one -- I mean I

1 think we're still left with the problem that it
2 is kind of a roulette when you refer to the
3 variability of the analytical method when the
4 variability of the natural product is just orders
5 of magnitude -- several orders of magnitude
6 bigger than the variability of the method. So
7 whenever we test something, it's simply going to
8 be a lottery whether it's going to be lower or
9 higher just because we choose one leaf rather
10 than another one. So we are really in a jam
11 there.

12 MR. CECIL: We have to work with the
13 data that's provided to us. And that's what we
14 have to make our decisions based upon. And if
15 the analytical variability is a major component
16 and you have trend data that shows it, again we
17 will probably look at the data that demonstrates
18 the highest level of HPHC for both new and
19 predicate products. Because that was what caused
20 the greatest concern in terms of HPHC levels.

21 MS. JOHNSON: Thank you. So kind of
22 a related question, this question asks about in-

1 house laboratories. If they're not certified, is
2 the data that comes from these in-house
3 laboratories still acceptable for SE
4 requirements?

5 MR. CECIL: Certification is something
6 that allows us to have confidence in the data
7 that's presented. Again, we don't -- in the
8 absence of validation, certification gives us
9 some confidence. Validation is a superior way to
10 provide that information. And it isn't all that
11 expensive despite what those around you would
12 tell you, to provide a validation for each
13 individual method that is used to report your
14 HPHC content. So they are not absolutely
15 required. It is a good practice to be ISO
16 compliant.

17 MR. SCHEINESON: Just a related
18 question to that. Small businesses as you know,
19 use two or three of the same labs in the United
20 States. We've been seeing letters or -- NSC
21 letters issued because the applicant hasn't
22 furnished in detail the testing methods like

1 Global Apps uses, which is the same for everyone.
2 If there is some way of, you know, a right to
3 reference or acknowledging taking, you know,
4 notice that, you know, what they're testing
5 methods are, that would help.

6 MR. WALTERS: One way for the methods,
7 we can provide master files and cross reference
8 the methods. And then we don't have to look at
9 them every single time.

10 MS. JOHNSON: Thank you. That's
11 great. So when citing publically available
12 scientific articles, the question is, is it
13 always necessary to include copies of the entire
14 articles in submission?

15 MS. ROGERS: It's helpful to us so
16 that we know exactly which information the
17 applicant is wanting to reference. And then also
18 in addition to providing a copy of the article in
19 an appendix please, it would be very helpful for
20 you to explain how that article or the data
21 within that article relate to your specific
22 product.

1 MR. SCHEINESON: Just one additional
2 question before you ask me to leave or our time
3 is up. These RFR products, removed from review
4 products, were expressly made, not predicates.
5 But there are 1,500 of those. And you know, the
6 question is, you know, why were they removed from
7 review so they might be used as predicates? And
8 is there some way that they could be used for
9 predicates? Or for instance, you know, just a
10 fact pattern. If someone buys one of these
11 predicates or owns one of these predicates and
12 just changes the label and the name of the brand,
13 you know, is that using it as a predicate? Is
14 that allowed? Is that the line extension under -
15 - you know, the Phillip Morris case?

16 MS. ROGERS: So regarding the RFR
17 products, as we heard yesterday, if one of those
18 products were to be used as a predicate product
19 for a new SE report, we would pull it out of the
20 RFR queue and review it at that time so that it
21 could be used as a predicate product. So it's
22 not that the RFR products can never be used as a

1 predicate.

2 MR. SCHEINESON: That's a huge
3 disincentive, you understand.

4 MS. JOHNSON: Thank you. We had a
5 question about recreated predicates. It's a
6 little long, so bear with me. It says recreated
7 predicates will by definition test differently
8 than the actual predicate cigarettes because at
9 minimum, the tobacco would be different based
10 upon natural variability. In addition, in some
11 cases, the paper banding material and other
12 materials used in the predicate may no longer be
13 available. How would the manufacture and testing
14 of a recreated predicate help FDA make an SE
15 decision under these circumstances?

16 MR. CECIL: Will the real chemists
17 please -- No. In the cases where there is a
18 material that is different, it is no longer a
19 recreated predicate. It is a surrogate product
20 at that point. If for whatever reason you've had
21 to use a different paper because it's not
22 available, understood. And we would expect or

1 hope to see information from the applicant
2 stating what the differences are, making it clear
3 to us what they are. So that we can evaluate
4 whether or not those would or would not cause us
5 to have concern about the use of the data from
6 that surrogate product in reference to the
7 predicate product.

8 We do acknowledge and we have accepted
9 surrogates for the evaluation of data where the
10 surrogate and the predicate product are not
11 identical. This is not necessarily unusual. But
12 we need to know what we're looking at. And too
13 often we've received applications that say this
14 is the surrogate product and here's the data
15 without any information about the design, about
16 the tobacco blend, about the ingredients
17 included. No indication to allow us to make a
18 comparison as to whether the surrogate and the
19 predicate are the same. And that puts us in a
20 difficult situation in saying now can we use the
21 data we've received, which we'd like to use, for
22 the comparison? We want to complete the

1 application and make the evaluation. But if we
2 cannot make a comparison, we cannot accept that
3 surrogate product.

4 MS. JOHNSON: Thank you. Do you have
5 something more?

6 MR. SCHEINESON: If there are no other
7 questions, you might want to submit questions
8 here.

9 MS. JOHNSON: We have a couple more.

10 MR. SCHEINESON: The outside world
11 sort of is curious what CTP does to ensure
12 consistency between application reviews to make
13 sure that everybody is being treated the same.

14 MS. JOHNSON: We're waiting for me.
15 So sorry. Go ahead.

16 MR. CECIL: We have a number of things
17 that we do. Obviously any time you're dealing
18 with a lot of reviewers, we do have a group of
19 TPLs we work together and discuss these things
20 that are going on. We work with the individual
21 reviewers and talk to them about what sorts of
22 things we want to see.

1 There are several review processes
2 internally to ensure that we're being consistent.
3 These are not one offs that we just whip out the
4 TPL and send it out there. There's a lot of
5 people who look at it. And look at previous
6 judgements on individual materials. Now keep in
7 mind, every cigarette or every smokeless product
8 that we compare stands on its own merit and needs
9 to be evaluated on its own merit. And we do make
10 every attempt to be consistent in how we evaluate
11 these things.

12 MR. SCHEINESON: For not substantially
13 equivalence orders, do those have a higher level
14 of review before they're issued? It just seems
15 to be this week that I've gotten a lot of those.
16 Maybe I'm going to get more after this session.

17 MS. ROGERS: No. We use the same
18 level of review for all reports. And we've
19 described today some of the common issues that
20 we've seen and just our recommendations for how
21 to consider them and address them. But we don't
22 consider the reports beforehand. You know, we

1 review them all in a similar manner before we
2 even know the final designation of SE or NSE.

3 MS. JOHNSON: Thank you.

4 MR. CECIL: And I would go even a step
5 further and say we're not anti-industry. We're
6 not trying to NSE things. And the reason we take
7 the SEs and the NSEs through a similar route is
8 that we also have folks on the other side, the
9 watchdogs watching to make sure we're not
10 approving things that are inappropriate. It's
11 very important that we evaluate good products, or
12 at least consistent products with inconsistent
13 products in terms of new versus predicate.

14 MR. SCHEINESON: Just from a guy that
15 has scars over his body. In this regard, you're
16 now being much more specific with what these
17 applications need to contain. You know, it's
18 helpful. And a lot of it is expensive and time-
19 consuming. But how are you going to help
20 companies that might be at that last stage in the
21 P-find letter or you know had a 60 day review
22 time for an A/I or a 30 day for a P-find, but now

1 understands this information and can get it, but
2 needs some time and some ability to do that. How
3 can you help them?

4 MS. ROGERS: So as we heard from the
5 speakers yesterday, we have changed our process
6 recently to allow much longer times for any
7 deficiency letter. So rather than the 30 days or
8 60 day response time, now each deficiency letter
9 will have, I believe it's 180 day response time.
10 So the applicants will have a much longer time to
11 work to address those issues that are brought up
12 in the deficiency letters.

13 MR. SCHEINESON: I've gotten those
14 letters or my clients have gotten those letters
15 for products that have not yet been referred to
16 scientific review in the event they want to
17 consider predicates, but not for those that are
18 in scientific review. Are those letters -- will
19 those be 180 days too once they've --

20 MR. HOLMAN: So a lot of the questions
21 being discussed here were addressed yesterday.
22 And I'm going to kind of cut off the

1 conversation. I'm not as nice as Eshael, but we
2 have a stack of cards -- I mean a stack, and we
3 haven't gotten to hardly any of these. So I want
4 to make sure -- I'm going to kick things off by
5 getting a couple of cards I got personally. And
6 I'll ask the question and then respond and then
7 Eshael will come back up and ask some additional
8 questions on the stack of cards here.

9 Actually I got two cards that are
10 somewhat -- I'm going to have a similar response
11 to both. One was about the studies I referenced
12 and making those publically available to
13 manufacturers. And the other was basically
14 discussion again of internal guidelines and
15 making those available to public.

16 In terms of the studies, we do publish
17 those studies in peer reviewed journals. We've
18 published a couple. We have a couple more in
19 works. And then we have some ongoing studies
20 that aren't quite at the publication stage, but
21 they are ongoing. And as soon as we get those
22 results, we will publish them and share the

1 results of those.

2 Some of you guys may be aware that we
3 have some internal policy memos. We have
4 released those under FOIA, but we are looking to
5 actively post them on the website to make them
6 available to all stakeholders and not just a
7 select few. That is in process. I hope in the
8 not too distant future, we'll make those
9 available. And I think those will be very
10 useful. They will outline for a given policy or
11 issue what our evaluation of the data is and
12 where we landed on, you know, what data may or
13 may not be necessary for a given difference in
14 characteristics between the new and the predicate
15 products. So with that, I'll turn it back over
16 to Eshael.

17 MS. JOHNSON: Thank you. So actually
18 the panel has been answering some of the
19 questions that we've gotten from the audience.
20 I've been trying to integrate them into the
21 questions when the topic came up. I'm like oh
22 let's slide in the HPHC question. Let's slide in

1 the stability testing question.

2 There are a couple -- I think one
3 other formal question. I don't know if others
4 have any, but we only have five more minutes left
5 for the panel, so I wanted to ask that question.
6 And give folks an opportunity for one other
7 comment that they may have.

8 This last question was specifically to
9 your presentation, Dr. Rogers. On Slide 33, they
10 ask may stability testing be conducted under
11 accelerated conditions?

12 MS. ROGERS: So the type of stability
13 testing that was discussed in my presentation
14 generally refers to smokeless tobacco products.
15 And some of that stability has to do with
16 microbial activity in the product. And
17 unfortunately that type of testing cannot be done
18 under accelerated conditions like chemistry
19 testing could be.

20 MS. JOHNSON: And I lied, I did have
21 one other formal question. This question says
22 that in information request letters from FDA,

1 they've suggested that cigar bands, which is
2 paper cigar boxes made of wood, et cetera are
3 important characteristics for compiling new and
4 predicate -- yes, I think that's compiling new
5 and predicate handmade cigars. Does FDA still
6 believe this to be the case? Please explain how
7 it affects characteristics.

8 So it sounds like they're asking how
9 the paper and the wood would actually impact the
10 product of the cigar itself.

11 MR. CECIL: It will depend upon the
12 paper and the inks and the type of wood and what
13 is absorbed through that wood. In many cases,
14 things that are in direct contact, it would be
15 dealing with them just like it was a packaged
16 product. And so any -- in this case, paper band
17 added to a cigar might have leaching of the inks
18 through the paper into the cigar itself. The
19 same would go with the wood. The wood that's
20 chosen generally is relatively volatile. And
21 that volatile component may be absorbed by the
22 cigars as well.

1 Again, we have not evaluated to my
2 knowledge, anything having to do with these. So
3 until we actually see a submission, it's going to
4 be hard for us to make any clear assumptions
5 about what we will do.

6 MS. JOHNSON: That's the last
7 question. I thank the panel for your comments.
8 It was a spirited and lively discussion. Kept us
9 awake first thing this morning. Let's have a
10 round of applause for our panel. We are now
11 going to take a 15 minute break. If we could be
12 back here and in our seats about 10:45, that
13 would be great. Thank you.

14 (Whereupon, the above-entitled matter
15 went off the record at 10:28 a.m. and resumed at
16 10:45 a.m.)

17 MS. RUDOLPH: Okay, folks, we're going
18 to go ahead and get started. I did try to call
19 folks in from the hallway, so we'll give them a
20 minute here to kind of roll their way through and
21 get settled. So just for those of you who were
22 not able to join us here in the meeting in person

1 yesterday, just a reminder, on the last page of
2 your agenda, there's some really helpful
3 information.

4 I think one of the things that's
5 important to note, that if you weren't able to
6 see the sessions that took place yesterday, which
7 were foundational to the conversations today,
8 that you'll be able to watch that -- not in real
9 time, obviously -- but you'll be able to watch
10 the tape versions of the webcast, and then soon,
11 what will follow, as stated on the back here, in
12 terms of the other meeting resources.

13 We'll be having a transcript, as well
14 as all of the presentations, in time, will be
15 made available on our website. So future notice
16 for you, just to keep track of what we're trying
17 to provide you, and keeping you in the loop on
18 what's happening here today.

19 As we settle in, I'll just state that
20 we're coming into Session number 9, and we will
21 be covering -- no, let me see. Am I in the right
22 place? Session number 7, excuse me. Look at me

1 getting ahead of ourselves.

2 So before lunch, we'll have an
3 opportunity to hear from Dr. Murphy and Dr.
4 Apelberg, who will both be addressing issues
5 related to tobacco product applications, one
6 dealing with pre-market, and the other dealing
7 with the MRTP applications. So without further
8 ado, Dr. Murphy.

9 MS. MURPHY: Good morning. I'm Iilun
10 Murphy. I'm the director of the Division of
11 Individual Health Science, and I'm going to be
12 talking to you about pre-market tobacco product
13 applications, PMTAs.

14 So to briefly review, the 2009 Tobacco
15 Control Act provides FDA authority to regulate
16 tobacco products. Before a new tobacco product
17 can be legally marketed, a PMTA must be submitted
18 and determined to be appropriate for the
19 protection of public health -- and I'll be
20 calling that APPH, for short -- so that it may be
21 introduced into interstate commerce. Unless the
22 product is found to be substantially equivalent,

1 SE, to a predicate tobacco product, or the
2 product is found to be exempt from SE.

3 Yesterday, Nick Hasbrouck described
4 the PMTA process with a focus on the
5 administrative aspects, and today, I'll be
6 focusing on the scientific content. So with
7 respect to PMTAs, to understand if a new tobacco
8 product is APPH, FDA must evaluate a product's
9 impact on the population, as whole, meaning
10 current tobacco product users, as well as non-
11 users.

12 Current tobacco product users are a
13 broad category. For example, a current tobacco
14 product user may be an electronic cigarette user,
15 a smoker, or a poly-tobacco product user. Each
16 of these types of current tobacco product users
17 may have varying health risks.

18 As such, it is important for
19 applicants to define populations, especially in
20 the context of study design. Let's also consider
21 non-users. Non-users may be an individual who
22 had not previously used tobacco products, who

1 experiment or initiate tobacco product use, or a
2 non-user may be those individuals who do not use
3 tobacco products, but are exposed to tobacco
4 toxicants via second or third hand exposure.

5 In day one of the workshop, Nick
6 Hasbrouck reviewed the 910(b)(1) contents of a
7 PMTA, so I won't go through these bullet points
8 again in detail. I do want to point out that
9 it's important for applicants to ensure the PMTA
10 addresses each of these points adequately, as
11 they relate to Section 910(c)(2) of the Tobacco
12 Control Act, which list the bases to deny PMTAs.

13 These are, one, lack of showing that
14 permitting marketing of tobacco products is APPH,
15 two, methods used in or the facilities or
16 controls used for the manufacture, processing, or
17 packing of tobacco products do not conform to
18 requirements of 906(e), which are currently not
19 in existence, three, proposed labeling is false
20 or misleading, and four, the tobacco product does
21 not conform to tobacco product standards in
22 effect under 907, and there's a lack of

1 justification for the deviation.

2 There are currently no tobacco product
3 standards, other than the special rule for
4 cigarettes related to characterizing flavors.

5 And pertaining to the last bullet
6 point here, Dr. Hoshing Chang discussed in detail
7 other information relevant, such as the
8 environmental assessment, and recall that the
9 environmental assessment, or the EA, as a
10 National Environmental Policy Act requirement, is
11 not actually a part of the integrated scientific
12 evaluation of a new product to determine if the
13 product is APPH.

14 However, an EA is part of a marketing
15 order decision. It is a public standalone
16 document that assesses the significance of a
17 proposed action's environmental outcomes. And
18 for your consideration, there are two draft
19 guidances available relevant to PMTA submissions.

20 These draft guidances are not FDA-
21 implemented policy. Rather, these guidances,
22 when finalized, will communicate FDA's

1 recommendations for submitting a PMTA, as well as
2 the general procedures by which FDA intends to
3 review a PMTA.

4 So let's move on to talking about
5 various scientific studies and analyses that are
6 helpful to support a PMTA. First, it's important
7 for FDA to understand what the proposed product
8 is and how it works.

9 To understand what the product is,
10 information relating to the product's parts is
11 useful. What is it made from, and how is it
12 manufactured?

13 The chemistry evaluation takes into
14 consideration information such as product
15 formulation, including HPHCs, chemistry design,
16 such as nicotine content, moisture, pH, tobacco
17 blend, and ingredients other than tobacco,
18 manufacturing steps and controls, performance
19 criteria and stability.

20 Of note, submitting protocols for HPHC
21 and other testing, not just the summary data,
22 assists FDA scientists in their review of

1 evaluating the HPHC and other test data. An
2 interesting question about ENDS product science
3 evaluation, and understanding how to evaluation
4 the potential aerosol constituents, as well as
5 the potential ranges of various constituents
6 among different users. That is: light use,
7 moderate use, and heavier use.

8 When studying cigarettes, it is
9 standard to evaluate cigarettes both using ISO
10 and Canadian Intense methods. But as you know,
11 ENDS don't have ventilation holes as cigarettes
12 do, and in this case, what primers would be
13 appropriate to adjust to study intense use and
14 non-intense use.

15 We have yet to have agreed upon
16 standardized measurements established for various
17 evaluation of ENDS products, therefore, it would
18 be helpful to have standardized matter to
19 understand aerosol content, as well as likely
20 range of delivery of emissions, taking into
21 account product characteristics, as well as user
22 behavior.

1 Whatever methods used to measure
2 aerosol emissions, considering the range of
3 product use, note that the last bullet point, it
4 is helpful for the submission to contain
5 sufficient details of supportive information
6 explaining the process used and the rationale, as
7 well as the results.

8 Product science evaluation also
9 involves looking at product design, principles of
10 operation, as well as manufacturing and
11 packaging. FDA currently does not have
12 requirements on reporting of design features
13 regarding specific tobacco products, such as
14 ENDS.

15 It's useful for FDA to have sufficient
16 information on the design and operation of the
17 tobacco product, such as the principles of
18 product design, which is the design parameters
19 that characterize the product.

20 Product operation, for example,
21 information on heating source and how the product
22 is supposed to be operated, and its ingredients,

1 as well as components in understanding how all of
2 these interrelate.

3 Taking an ENDS product into
4 consideration, how does the temperature to which
5 an e-liquid is heated impact the chemistry of the
6 e-liquid and the aerosol? The information can
7 then allow for the development of a toxicological
8 profile, and understanding of user exposures and
9 potential impact.

10 Additionally, it is important to
11 understand that a product can be manufactured
12 consistently with quality assurance. For
13 example, in ENDS products, you may want to
14 consider whether and how to conduct testing to
15 span the available operating conditions of the
16 proposed ENDS device. For example, temperature,
17 voltage, and liquid tank fill status, if
18 applicable.

19 Another example to consider relates to
20 e-liquids. When describing the e-liquid,
21 consider including the e-liquid boiling point, as
22 well as the e-liquid viscosity at room

1 temperature.

2 And in addition, consider providing an
3 explanation of the e-cigarette configuration used
4 for e-liquid testing, and why that configuration
5 was chosen, and how it compares to those
6 currently on the U.S. market. As described in
7 the PMTA for ENDS draft guidance available for
8 comment, applicants may send at least one sample
9 of the new finished product.

10 If a PMTA is sufficient to progress to
11 a substantive scientific review, FDA scientists
12 will make a preliminary determination on the
13 likely number of samples to be submitted for FDA
14 to conduct its own testing and analyses. FDA
15 will send the applicant a letter requesting a
16 specific number of samples to be submitted, and
17 instructions on how to submit the samples.

18 As mentioned in the PMTA talk given by
19 Nick Hasbrouck yesterday, we do encourage
20 applicants to consider submitting a pre-
21 submission meeting request with CTP to discuss
22 appropriate submissions of samples for your PMTA.

1 The draft guidances on PMTA state the
2 following information is helpful to assess the
3 non-clinical health risks information of a new
4 tobacco product such as identification of
5 potential human health risk that focuses on
6 exposures to users, the evaluation of ingredients
7 includes leachables and extractables, and there
8 is also a list of useful considerations to
9 include as part of the toxicological evaluation.

10 In general, when evaluating ENDS
11 products, toxicity profiles via the inhalation
12 route, it's useful to consider all ingredients
13 and components added to a product, as well as the
14 potential heat degradation byproducts that may
15 form during use.

16 Consumers of ENDS products have
17 simultaneous exposures to more than one chemical,
18 and therefore, the public health risks associated
19 with the product use can vary, depending upon the
20 number and type of chemicals, that is
21 carcinogenic versus non-carcinogenic present in
22 the e-liquids or aerosols.

1 For a toxicity study conducted
2 prospectively, it's useful when, as stated,
3 studies focus on the potential human exposure of
4 the product. Thus, exposures that mimic the
5 highest consumer use scenario and lower exposure
6 level in the toxicological studies are helpful
7 evaluations. And based on the results
8 determined, analysis of constituents' toxicant
9 levels at that exposure tested can also be
10 included.

11 If the consumer can change the voltage
12 or temperature of the heating element, consider
13 providing any available data on the subsequent
14 changes of the aerosol ingredients, and please
15 also consider including any toxicity information
16 relevant to the exchanges.

17 It's useful if you provide
18 aerosolization and properties of each of the
19 ingredients. For example, constituents,
20 humectants, metals, flavors included, the
21 particle size of these ingredients, and
22 deposition of these particles through inhalation.

1 Also consider discussing how these
2 properties could affect the product's toxicity
3 profile. FDA supports reducing the reliance on
4 animal testing or adequate and scientifically
5 valid non-animal alternative studies substituted.
6 And FDA encourages meetings with sponsors early
7 in the developmental process to discuss what, if
8 any, animal testing is appropriate, and the
9 suitability and acceptability of non-animal tests
10 of their particular new tobacco product.

11 When animal-based non-clinical
12 laboratory studies are conducted, investigators
13 should use appropriate animal models, and adhere
14 to the best practices of refinement, reduction,
15 and replacement of animals in research, and to
16 applicable laws, regulations, and policies
17 governing animal testing, such as the Animal
18 Welfare Act, and public health service policy of
19 humane care in use of laboratory animals.

20 The draft guidance on PMTA proposes
21 that a PMTA comparison of the new tobacco product
22 to a representative sample of tobacco products

1 legally on the market.

2 When discussing comparative product
3 information, it's important to have justification
4 in your PMTA regarding why using data from
5 certain other products to support your PMTA is
6 appropriate.

7 The tobacco product market can be
8 considered in many ways, and applicants may want
9 to consider what is or are the most appropriate
10 comparators from the various tobacco products on
11 the market. The most appropriate tobacco product
12 comparators are likely to be the potential users
13 of your proposed product already used.

14 So for considering an ENDS, for
15 example, manufacturers typically state that the
16 target consumer is the current smoker, in which
17 case, cigarettes could be an appropriate
18 comparator. Also, it would be likely that
19 current ENDS users may consider your new proposed
20 tobacco product, therefore, other ENDS products
21 on the market could also be an appropriate
22 comparator.

1 To address comparisons of ENDS use to
2 smoking conventional cigarettes, applicants may
3 consider using differences that could impact the
4 user's exposure to constituents of toxicological
5 concern that may result in adverse health
6 effects. That is to say, that it is helpful to
7 consider the manner of use, duration, and
8 frequency of use, and the settings of the
9 environment.

10 For example, outdoor use versus indoor
11 space use, in which the tobacco products are used
12 when comparing products. And unlike an SE
13 application, in this setting, a more general
14 comparison in terms of understanding ranges of
15 exposures, use, health impact, is helpful.

16 For example, the proposed new ENDS
17 product has a nicotine concentration of X, as
18 compared to general nicotine concentrations of
19 other ENDS and cigarette products that are
20 generally from the range of Y to Z. Of interest
21 is how your product's concentration compares with
22 the range available, and its impact.

1 The draft guidance on PMTA proposes
2 applicants consider including the following
3 information to assess the human health impact of
4 a new tobacco product.

5 The evaluations of the likelihood of
6 initiation of cessation by both users and non-
7 users, which may include evaluations of
8 perceptions as product risk, both absolute and in
9 comparison to other tobacco products, as well as
10 to quitting all tobacco products, of use
11 liability and addictiveness, evaluation of
12 product use patterns, for example, topography,
13 frequency of use, and use by demographics,
14 evaluations of acute and long-term health effects
15 may use biomarkers, health outcome measurements,
16 as well as other endpoints. And labeling
17 comprehension and human health factor issues
18 impacting product use and misuse.

19 Initiation and cessation are defined
20 in different ways. It's useful if clear
21 definitions and rationale are provided for how
22 they are being defined in any particular setting

1 in order to support meaningful interpretation of
2 research findings.

3 FDA acknowledges that it may not be
4 feasible to directly measure the rate of uptake
5 of a new tobacco product in a population,
6 especially if it's never been on the market.

7 Even if a product is on the market, there may not
8 be sufficient number of users to directly study
9 initiation in an observational setting.

10 However, there are many different
11 types of studies and lines of evidence that could
12 provide information about the likelihood that
13 existing users will stop, or non-users will start
14 using tobacco products. These include, but are
15 not limited to: studies of factors that may
16 predict future tobacco product use uptake, such
17 as consumer perceptions and behavioral intention
18 studies, observational studies of behavior, which
19 could include cross sectional studies to assess a
20 snapshot in time, such as the national surveys or
21 prospective studies which follows individuals
22 over time to assess behavior change and the

1 factors that influence such change.

2 Several randomized clinical controlled
3 trials of products which outline existing tobacco
4 users have been conducted to assess the extent to
5 which e-cigarettes may facilitate cigarette
6 quitting, as an example.

7 Abuse liability studies are studies
8 designed to assess the extent to which a product
9 may result in addiction, and typically include
10 subjective measures of product appeal, which
11 could provide insight to the extent to which a
12 product may be taken up by current cigarette
13 smokers.

14 Market research studies, which may be
15 both quantitative and qualitative, are designed
16 to identify and characterize the potential market
17 and consumer preferences related to a new tobacco
18 product. For example, sales data from foreign
19 market experience or similar products in the US
20 market can provide useful information as well.

21 General principles suggest that
22 multiple lines of evidence, which strengthen an

1 argument related to the likelihood of tobacco
2 product initiation and cessation.

3 I'm going to move on to talk about
4 specific types of human studies now, and I'd like
5 to start this section by discussing consumer
6 perception studies. Understanding the health
7 risk of a product can be informed by evaluating
8 the perception and appeal of a product, and its
9 impact on behavior intentions and actual
10 behavior.

11 One area of interest is understanding
12 how perceptions and appeal of a specific product
13 might be generalized to other products within the
14 same brand family, or to other similar products
15 of other brands. For example, research suggests
16 that flavors are associated with initiation and
17 continued use of tobacco products -- particularly
18 among youth and young adults -- and may impact
19 consumer perceptions and use behavior.

20 Some products even from the same brand
21 family may have different impacts on population
22 health. Thus, consider providing information on

1 each flavor to demonstrate how consumers perceive
2 the product and its flavor, as well as its impact
3 on intention to use the product, as well as the
4 actual use of the product.

5 Qualitative research provides insights
6 into individuals' thoughts, feelings, and
7 behaviors, and can serve as useful evidence in
8 understanding the product's potential impact once
9 it's on the market.

10 Studies of consumer perceptions
11 generally follow established methods, such as the
12 use of best practices for questionnaire design to
13 avoid bias and to ensure that the data collection
14 is valid.

15 In addition, the size of the sample in
16 these types of states can vary depending on the
17 research question, but usually a clear rationale
18 for the sample size is given based on practical
19 considerations, statistical power to detect
20 differences, and other factors.

21 The use of validated items, wherever
22 possible, allows for the data collected to be

1 compared to other studies, and also ensures that
2 the data collected are measuring what they are
3 intended to measure.

4 Along those lines, clearly define aims
5 that are specified before data collection begins
6 allows for transparency. Overall, a clear
7 explanation of the methods and samples included
8 in the study allow others to better understand
9 the results in context. And as in all studies
10 with human subjects, these studies consider
11 protection of human subjects as a critical
12 element.

13 Finally, reports of these studies such
14 as those found in the scientific literature
15 include a full reporting of the study protocol,
16 the measures used, recruitment strategy, and
17 sampling, sample characteristics, analysis, and
18 other aspects of the study to allow for a full
19 and complete understanding of the study, the
20 results and the conclusions, based on the
21 results.

22 Applicants have asked if youth

1 behavioral data are required by the FDA for PMTA
2 authorization. The answer is that the FDA does
3 not require youth behavioral data at this time.
4 However, information to allow FDA to evaluate how
5 the proposed new product may influence tobacco
6 initiation and use among youth is useful to
7 determine if the product is APPH.

8 Inferences regarding youth may
9 potentially be extrapolated from young adults, as
10 well as derived from market data, reviews of
11 published scientific literature, national
12 surveys, or bridging information obtained from
13 other sources.

14 If an applicant takes such an
15 approach, the draft guidance proposes that the
16 applicant clearly explain how such data can be
17 extrapolated to youth for the specific products
18 that are subject at the PMTA submission.

19 Abuse liability testing may offer data
20 and information to support an understanding of
21 the likelihood of initiation and cessation of
22 tobacco products.

1 Traditional abuse liability
2 assessments are designed to evaluate likelihood
3 of abuse, and can also assess consequences of
4 abuse. Determination of a product's abuse
5 potential can be accomplished, again, through
6 multiple lines of evidence.

7 Common principles to consider in
8 pharmacology studies are listed here, detailing
9 some information on study design and information
10 helpful for FDA science reviewers in a PMTA. For
11 example, explanation of selection of prescribed
12 puffing regimens, rationale for selection of
13 comparative products, and making sure that study
14 limitations are clearly identified.

15 It is a statutory requirement in order
16 to authorize a PMTA that the proposed labeling is
17 not false or misleading. A label comprehension
18 study evaluates whether consumers understand the
19 key label messages and communication of
20 information.

21 The general design concepts to
22 consider are: to establish primary communication

1 objectives, specify study designs that meet
2 objectives and calculate appropriate sample size,
3 enroll in appropriate population, specifying your
4 target demographics, vulnerable populations,
5 literacy level, and construct a questionnaire
6 that targets the objectives.

7 Set a priori target thresholds that is
8 correct answer to the question. A target should
9 be established for each communication objective.
10 And using test labeling as close as possible to
11 your final labeling is most useful.

12 Going back to thinking about the
13 proposed product itself, human factors are
14 important to consider when designing a product.
15 Human factor considerations assess if users will
16 be able to operate the product appropriately by
17 focusing on the interaction between people and
18 products.

19 Risk management consideration controls
20 for potential hazards that might occur,
21 considering the user, product interface with a
22 goal of minimizing use-related hazards. Human

1 factor studies allow for evaluation of use
2 behavior factors that can help to reduce error,
3 adverse events, and product recalls.

4 Even with the best of intentions,
5 sometimes you just don't know what people might
6 do until you have them actually try a product.
7 So early prototype testing of human factors may
8 assist in improvement of product design.

9 Importantly, when considering a new
10 proposed product, FDA seeks to understand the
11 likely impact on human health. This can include
12 the comparative health risks posed by the
13 proposed tobacco product, and may also involve
14 considering poly-tobacco product use.

15 For example, what is the change in
16 health risk of a smoker who completely switches
17 to a specific ENDS product -- which is the
18 subject of the PMTA -- as well as compared to
19 switching to other ENDS products on the market?
20 And what is the change in health risk if the user
21 transitions to poly-tobacco product use, such as
22 continuing to smoke and use the new proposed

1 product?

2 To evaluate the acute and chronic
3 health effects associated with the proposed
4 product, or poly-tobacco product use, the draft
5 guidance out for public comment recommends
6 applicants include studies, other scientific
7 evidence, or both, that identify biomarkers of
8 exposure, biomarkers of harm, and health outcome
9 measurements or endpoints. And I'll talk a
10 little bit more about biomarkers in the next
11 slide.

12 Data to support the impact of the new
13 tobacco product on health of users and non-users
14 may include health effects related to the
15 specific constituents that have been identified.
16 For example, for ENDS, in aerosol constituents
17 delivered to the user.

18 These constituents will vary,
19 depending on the product, and may include
20 glycerine, propylene glycol, and nicotine,
21 flavorings and metals. Relevant data may include
22 health effects of aerosol exposures, including

1 changes in the physiological measurements, such
2 as heart rate and blood pressure, changes in
3 lung, cardiac, and metabolic function. Adverse
4 experiences, such as throat irritation and cough,
5 and changes in laboratory values, such as
6 mediators of inflammation and complete blood
7 count indices.

8 When designing studies, it's helpful
9 if the study findings are generalizable to the
10 population of U.S. users and non-users, as
11 appropriate, of your new tobacco product. If
12 you're relying on the published reports to
13 support your PMTA, consider justifying why the
14 data from those reports can be bridged to your
15 product, and are appropriate for determining the
16 impact of the new tobacco product on the U.S.
17 population that are the likely consumers for your
18 product.

19 In terms of individual risk, we are
20 seeking to understand the product's health impact
21 on users, the actual consumers and non-users,
22 which may be set through secondary and tertiary

1 exposures.

2 Clinical endpoints are the gold
3 standard of understanding the impact of a product
4 on the health. However, clinical endpoints can
5 take years, decades, to develop. So appropriate
6 biomarkers may serve as a substitute endpoint,
7 and have the potential to correctly predict
8 clinically meaningful endpoints in the interim.

9 Applicants have asked: what biomarkers
10 are useful to measure when evaluating tobacco
11 products such as ENDS? And as with all
12 biomarkers, those that are specific to the
13 exposure, and of changes that are clinically
14 relevant are most useful.

15 At this time, there's not an agreed
16 upon panel of biomarkers established to
17 understand ENDS's impact on human health. There
18 are different kinds of biomarkers that can be
19 measured.

20 Issues to consider include asking, for
21 example, an ENDS product may include, what are
22 the known ENDS characteristics, and what

1 exposures and potential harm are likely
2 anticipated worth evaluating? What is the likely
3 nicotine exposure for the user, and do various
4 flavorings or other ingredients impact nicotine
5 exposure?

6 This could be a direct chemical
7 interaction, or it could be through a metabolic
8 interaction. Sorry. We have some understanding
9 that factors, such as nicotine concentration,
10 voltage, puffing behavior, impact nicotine
11 exposure. Thus, evaluating such parameters is
12 likely helpful in understanding the range of
13 nicotine exposure.

14 And recall that when evaluating
15 potential risk of a proposed product, the statute
16 itself requires that applicants show the health
17 risks of the tobacco product, and whether tobacco
18 product presents lower risk than other tobacco
19 products.

20 Applicants have also asked: what
21 studies are required for a PMTA? There are
22 specific study requirements for a PMTA, and it

1 may be possible to support a marketing order for
2 an ENDS product, as an example, without
3 conducting new non-clinical or clinical studies,
4 given other data sources can support the PMTA,
5 and provide sufficient information to inform FDA
6 that the product is appropriate for the
7 protection of public health, APPH, and address
8 the other 910(c)(2) issues discussed earlier.

9 In most situations, it is likely that
10 at least some analytical testing specific to the
11 product would be conducted to support a PMTA. If
12 you have a product currently available on the
13 market, it is possible that research has been
14 done on the product, or your product is similar
15 to other products, which are publicly available
16 and are a subject of research studies, in which
17 case, you may submit the available information,
18 along with bridging information to justify the
19 use of such underlying studies.

20 If conducting studies, alternatives to
21 the traditional randomized controlled clinical
22 trials, which are typically used for drug

1 development, may be appropriate to support a
2 PMTA.

3 Also, various clinical studies such as
4 pharmacokinetic, pharmacodynamic, or biomarker
5 studies, topography studies, focus group studies,
6 et cetera, as discussed earlier, can be
7 supportive of a PMTA.

8 I've discussed bridging a few times in
9 this presentation, and the importance of
10 providing rationale and justification to support
11 bridging when this is being used. It's likely
12 that most PMTAs will include various data sources
13 to support the submission.

14 Some of these examples are published
15 peer-reviewed literature, analyses of existing
16 national data sets, such as NATS, NYTS, PATH, and
17 may also include some original scientific
18 investigations.

19 When conducting a literature review,
20 the literature reviews have scientific
21 information that are publicly available.
22 Scientific reviews interpret results in a context

1 of study methods, and the experimental conditions
2 that generate the results. So significant
3 results from a study poorly designed may not be
4 as strong evidence as suggestion of a positive
5 association in a study with much more rigorous
6 study methods.

7 Explaining how cited literature is
8 relevant to the proposed product, or to the
9 comparison between the proposed product and
10 comparative products is helpful for the FDA
11 review. And describing methodologies used for
12 conducting literature review and how the
13 literature was evaluated is useful to include in
14 the PMTA.

15 And finally, moving into the FDA PMTA
16 review and some lessons learned. I have
17 reiterated that the FDA must determine if the
18 proposed product is APPH, appropriate for the
19 protection of public health.

20 Applicants must address the statutory
21 requirements, as appropriate, pertaining to the
22 PMTAs in the end. To facilitate review, consider

1 including a one or two-sentence description that
2 highlights the key product characteristics and
3 study results that you believe would make the
4 marketing of the product APPH.

5 For example, the product delivers
6 significantly lower levels of specific HPHCs to
7 users than tobacco products that are currently,
8 they are currently consuming.

9 Having a summary in the beginning,
10 touching on the various aspects outlined
11 throughout this talk, such as product
12 characterization, toxicological profile, user
13 behaviors, and human health impact helps orient
14 the reviewers and facilitate review.

15 The following are some questions that
16 FDA has discussed in deciding whether a product
17 is APPH. Are the levels of HPHCs and other
18 constituents of toxic concern in the new tobacco
19 product similar or lower than levels of similar
20 tobacco products or other appropriate competitor
21 tobacco products currently on the U.S. market?

22 Does the scientific evidence provided

1 in the application support that the use of the
2 tobacco product has a lower risk of disease for
3 the individual than the use of other similar or
4 appropriate competitor tobacco products currently
5 on the U.S. market?

6 Does the scientific evidence provided
7 in the application support that the use of the
8 tobacco product has a lower risk of disease for
9 the individual than the use of other similar or
10 appropriate competitor tobacco products on the
11 market?

12 Will the marketing of the new tobacco
13 product affect the likelihood of non-user uptake,
14 cessation rates, or other significant shifts in
15 user demographics in a manner to decrease
16 morbidity and mortality from tobacco product use?

17 It is the applicant's responsibility
18 to provide scientific evidence and justification
19 to support that the product is appropriate for
20 the protection of public health.

21 Here are some examples of challenges
22 seen by FDA reviewers. There is no environmental

1 assessment provided in the submission. A
2 submission is sent in a format that the FDA
3 cannot process. For example, it's password-
4 locked, and the password is not provided. There
5 is insufficient product identifying information.
6 FDA receives large PMTA submissions. FDA
7 reviewers spend considerable time locating
8 information within the FDA, the FDA PMTA
9 submission that is needed for their scientific
10 review.

11 So therefore, a well-organized table
12 of contents and functional hyperlinks really help
13 the reviewer go through the submission.

14 Applicants have sent new study data and large
15 amendments to FDA for review towards the end of
16 the FDA scientific review phase. So reviewing
17 additional information has caused delays in FDA
18 issuing of marketing or no marketing order.

19 Lastly, on this slide, I have
20 additional examples of review challenges. FDA
21 reviewers have observed the following issues
22 during the PMTA review. Omissions of protocols

1 and methodology validation reports, missing data
2 from non-clinical and clinical studies.

3 For example, data might be referenced,
4 but it's not included in the submission. Studies
5 submitted were conducted on a prototype of the
6 ENDS device, or other tobacco product, and not
7 the device actually subject of the marketing, and
8 bridging data is not provided to clearly link the
9 two different products. It can be difficult to
10 distinguish which version of the product is
11 intended for market, deciphering tobacco product
12 naming conventions.

13 And FDA has received PMTAs that
14 include incomplete information on ingredients,
15 product stability testing, design parameters,
16 manufacturing steps, manufacturing facilities.
17 So some, but not all facilities may be listed and
18 described.

19 The study design reports are not
20 included, even though a study may be mentioned in
21 the submission. And then, a panel of biomarkers
22 may be evaluated, but there's no rationale for

1 the selection of the biomarkers, and the results
2 are not interpreted.

3 What do you think the results mean in
4 terms of the impact on human health? If there
5 are differences in biomarker results between your
6 product and comparative products, what is the
7 significance?

8 I've discussed a lot of information in
9 a short time, and I hope you've found the
10 information provided helpful in your effort to
11 develop a quality PMTA submission. Here's a list
12 of additional resources related to PMTA
13 submissions, and of note, we had a two-day public
14 workshop on PMTAs about two years ago in October
15 2016, and it really goes into a lot more depth
16 about the different types of studies that would
17 be useful to support a PMTA.

18 So I think that if you're interested
19 in this topic area, going to that workshop
20 webinar might be helpful for you. Thank you so
21 much for your attention.

22 MS. RUDOLPH: And I just have a quick

1 announcement before Dr. Apelberg gives his
2 presentation. Following his presentation, we'll
3 go right into the panel before lunch instead of
4 after lunch.

5 MR. APELBERG: Oops. Okay. All
6 right. Good morning, everyone. My name is Ben
7 Apelberg. I am the director of the Division of
8 Population Health Science, in CTP's Office of
9 Science, and today, I'm going to be talking about
10 modified risk tobacco product applications.

11 So I'll start my talk today by going
12 over the standards for modified risk orders.
13 I'll then focus the majority of the presentation
14 on the approach that FDA takes to scientific
15 review, including the key scientific questions of
16 interest, and the types of evidence that could be
17 used to address them. Finally, I'll provide an
18 overview about FDA's experience to date, and
19 highlight some opportunities for clarification
20 and improvement moving forward.

21 So under Section 911(g)(1) of the
22 Federal Food, Drug, and Cosmetic Act, in

1 determining whether a modified risk order should
2 be issued, FDA must assess whether it has been
3 demonstrated that the product, as it is actually
4 used by consumers, will significantly reduce harm
5 and the risk of tobacco-related disease to the
6 individual tobacco users, and benefit the health
7 of the population as a whole, taking into account
8 both users of tobacco products, and person who do
9 not currently use tobacco products. We call this
10 a risk modification order.

11 And then, under Section 911(g)(2),
12 there's a description of a special rule for
13 certain products, which allows the FDA to issue
14 an order which we call an exposure modification
15 order for products that cannot receive a risk
16 modification order under Section 911(g)(1).

17 And the Act goes on to describe that
18 the FDA can issue such an order if it determines
19 that the applicant has demonstrated, among other
20 things, that the order would be appropriate to
21 promote the public health, that the label
22 labeling and advertising is limited to a claim

1 that the product does not contain or is free of a
2 substance, or contains a reduced a level of a
3 substance, or presents a reduced exposure to a
4 substance, that the scientific evidence is not
5 available and cannot be made available without
6 conducting long-term epidemiological studies for
7 an application to meet the standard that I just
8 mentioned on the previous slide under 911(g)(1).

9 The evidence, the scientific evidence,
10 however, that is available, demonstrates that a
11 measurable and substantial reduction in morbidity
12 or mortality among individual tobacco users is
13 reasonably likely in subsequent studies, and that
14 testing shows that consumers will not be misled
15 into believing that the product has been
16 demonstrated to be less harmful, or to present
17 less risk.

18 So the evaluation of an MRTPA can be
19 thought of in terms of a few key overarching
20 questions. The questions include, is there
21 adequate scientific substantiation of the
22 proposed modified risk information? What are the

1 health risks of the MRTP to individual tobacco
2 users? How do consumers perceive and understand
3 the modified risk information? And what are the
4 potential benefits and harms to the health of the
5 population as a whole that would be associated
6 with issuing a modified risk order?

7 Each of these steps involves the
8 evaluation of many specific questions, which
9 draws from multiple scientific disciplines, and
10 which I'll discuss further a little later in this
11 talk.

12 It's also important to keep in mind
13 some additional contexts for the MRTP pathway.
14 An MRTP order is an order for a specific product
15 with modified risk label, labeling, or
16 advertising. Therefore, all evaluation that
17 takes place in the context of an application for
18 a specific product with specific proposed
19 modified risk information that an applicant wants
20 to communicate about that product.

21 The applicant, it's the applicant who
22 proposes the specific modified risk information,

1 and the form and wording of a claim can have
2 critical impact on the final decision.

3 In April 2012, FDA announced
4 availability of draft guidance for modified risk
5 tobacco product applications. The contents are
6 shown here. This talk will provide additional
7 information relevant to the last four of these
8 bullets, which are, which are highlighted. And
9 when final, the guidance will represent the
10 agency's current thinking on modified risk
11 tobacco product applications.

12 Okay. The FDA reviews the scientific
13 information submitted in the MRTPAs to determine
14 whether the statutory requirements for
15 authorization provided in Section 911 of the
16 Federal Food, Drug, and Cosmetic Act have been
17 met.

18 In addition to the evidence presented
19 by the applicant, we'll consider recommendations
20 from the Tobacco Product Science Advisory
21 Committee, public comments, and any other
22 scientific evidence or information that is

1 available to the agency, including in the general
2 scientific literature.

3 In approaching the scientific review,
4 we consider a range of areas of focus. These
5 include, as I mentioned, substantiation of
6 modified risk information, relative health risks
7 to individuals, consumer understanding and
8 perception, and impacts to the population as a
9 whole.

10 And so I'll discuss this list a bit,
11 a bit more. But first, a preliminary step in the
12 evaluation is to identify the modified risk
13 information to be evaluated in the review. In
14 particular, FDA evaluates all information and
15 statements on the proposed label, labeling, and
16 advertising, as part of its scientific review.
17 This includes modified risk claims specifically
18 identified by the applicant in its request for
19 authorization, but also any other statements that
20 might appear in the proposed labels, labeling, or
21 advertising.

22 So now, I'll step through in a bit

1 more detail, the key areas of focus for the
2 review, which I just mentioned, and for each,
3 provide examples of the types of questions that
4 are considered in the review, as well as the
5 potential lines of evidence that may inform this
6 assessment.

7 So the first is substantiation of
8 modified risk information. Here, the question
9 is: is the proposed modified risk information
10 scientifically accurate? Depending on the nature
11 of the information or statement, there are
12 different types of evidence that might be
13 relevant to making this assessment.

14 This includes analyses of HPHCs of the
15 product, toxicological evidence, clinical
16 studies, and long-term epidemiological evidence.
17 In assessing relative health risks to
18 individuals, some questions include: what does
19 the evidence suggest about the potential health
20 risks of the product? How do the risks of the
21 product compare to never using, to cigarette
22 smoking, to other products in the tobacco product

1 category? How do the risks of complete switching
2 to the product compare to continued smoking,
3 quitting altogether, or quitting with the use of
4 FDA-approved cessation aids? Is there any
5 evidence of the potential for reduced exposure or
6 risk among dual users? What are the health risks
7 to individuals not using the product who may be
8 involuntarily exposed to the product?

9 And you know, once again, depending on
10 the nature of the product under review, the
11 evidence could be derived from toxicological
12 studies, from clinical studies, for example,
13 using biomarkers of exposure and potential harm,
14 and from long-term epidemiological studies.

15 In terms of consumer understanding and
16 perception, we consider questions like: what does
17 the available evidence suggest about consumers'
18 understanding of the modified risk information on
19 the product's label, labeling, and advertising,
20 and their perceptions of the product? What are
21 consumers' beliefs about the health risks of
22 using the product relative to other tobacco

1 products, which may include those within the same
2 class or same category?

3 Relative to the use of products in
4 conjunction with other products, so relative to
5 dual or poly-use, relative to the use of
6 cessation aids, and relative to quitting all
7 tobacco use?

8 The evidence for this assessment
9 typically comes from quantitative consumer
10 perception studies conducted by the applicant.
11 In terms of the assessment of the impact to the
12 population as a whole, we consider questions such
13 as: from the available evidence, what do we know
14 about who is likely to use the product, including
15 both intended and unintended users, and how they
16 are likely to use it?

17 How is the product likely to be
18 actually used by consumers? How likely is it
19 that consumers will not use the product as
20 intended or designed -- either intentionally or
21 unintentionally -- and what are the implications
22 of that type of use? Under what combinations of

1 product use behavior would we expect a net public
2 health benefit or harm? And are there specific
3 populations that would be at increased use of
4 using this product?

5 For these types of questions,
6 information can come from diverse lines of
7 evidence. So it may include actual use studies,
8 which may assess abuse liability, nicotine and
9 metabolite exposure, topography, and subjective
10 effects, such as product liking, consumer studies
11 that assess intentions to use, in particular,
12 after a consumers sees information about the
13 modified risk or modified exposure.

14 Epidemiological studies, which may
15 include surveillance data from other countries,
16 for example, as well as population modeling,
17 which, you know, can be used to attempt to
18 integrate different patterns of use and use
19 behaviors over time to assess the potential
20 impacts to the population.

21 When thinking about the population as
22 a whole, it's useful to consider groups based on

1 whether they are intended or unintended users of
2 the proposed MRTP. Here, we think of intended
3 users as really those could theoretically stand
4 to benefit from complete switching to the
5 proposed product. Often, this is current
6 cigarette smokers who are unable or unwilling to
7 quit.

8 In contrast, unintended users is
9 essentially everyone else for whom use of the
10 product would not yield a population health
11 benefit. To narrow this group, however, it's
12 useful to think about groups who are unintended
13 users, but may nonetheless be potentially likely
14 users.

15 For instance, this includes never
16 users, and in particular, most notably, youth,
17 who are particular risk of tobacco use
18 initiation. Recent former users, who may be at
19 high risk of relapse of tobacco use, and current
20 users of tobacco products that have a lower
21 toxicity profile than the proposed MRTP,
22 particularly those in the same general tobacco

1 product category.

2 Evaluation of an MRTPA, much like a
3 PMTA, also includes an assessment of a product
4 description and characterization. Here, in the
5 context of MRTPA, we think about questions like,
6 are the product design and composition
7 sufficiently described to offer full
8 understanding of what it is, how it is made, and
9 whether it is a product that can be manufactured
10 and distributed in a consistent manner? And does
11 the product design and composition raise any
12 additional concerns about individual health risk
13 or injury?

14 This evaluation may be based on
15 chemical analyses, engineering and microbial --
16 microbiological assessments. In addition, FDA
17 may also conduct independent laboratory testing
18 and site inspections.

19 One feature of the MRTPA pathway is
20 the involvement of the Tobacco Product Science
21 Advisory Committee, TPSAC. Per the statute,
22 FDA's required to refer all MRTPAs to TPSAC, and

1 TPSAC provides recommendations to FDA on the
2 MRTPAs.

3 Most meetings are open to the public,
4 either in person or via webcast, and provide the
5 public the opportunity to view the evidence and
6 discussion, as well as an opportunity to
7 communicate to the FDA, and to members during a
8 public comment period.

9 To focus the discussion, FDA brings to
10 the Committee select scientific issues from the
11 applications. Examples from our past meetings
12 include discussion of substantiation of modified
13 risk information, the relative health risks of
14 the product, consumer understanding and
15 perceptions of the proposed modified risk
16 information, and likelihood of product use.

17 Both FDA and the applicant prepare
18 briefing materials for the Committee, and present
19 at the meeting. Although FDA is not required to
20 follow TPSAC recommendations or votes, FDA does
21 take this information into consideration, along
22 with the other pieces of its assessment before

1 issuing a determination.

2 To date, FDA has held three TPSAC
3 meetings on specific modified risk tobacco
4 product applications. Another feature of the
5 MRTPA pathway is the requirement that FDA make
6 applications available for public comment. Those
7 are typically posted on a rolling basis,
8 including both the current application, as well
9 as amendments that come in during the review
10 process.

11 Applications are reviewed for
12 commercially confidential information are
13 redacted accordingly, prior to posting. To date,
14 we've posted over 1 million pages publicly across
15 the various applications. FDA makes available
16 for public comment all MRTPAs.

17 Any individual or organization can
18 submit either electronic or written comments to
19 the open docket. The public comment period is
20 typically open for at least 180 days on all
21 applications under review, and FDA will issue a
22 notice on the Federal Register announcing when

1 the comment period will close, which would be at
2 least 30 days from the date the last application
3 documents are posted.

4 When we look at the types of comments
5 that have been received to date, they're
6 typically comments across a range of areas, both
7 scientific and non-scientific, including some of
8 the points that are listed here. Comments are
9 also submitted from a variety of sources,
10 academia, public health groups, tobacco
11 manufacturers, tobacco retailers, et cetera. To
12 date, FDA has received over 300 public comments
13 across the MRTPA dockets.

14 So I've provided an overview of the
15 sources of information that inform the review, as
16 well as the areas of focus of the scientific
17 review, including some relevant questions and
18 lines of evidence that are informative.

19 Ultimately, the assessment involves
20 looking across the totality of the evidence to
21 consider the impact of a marketing order on both
22 the individual, as well as the population as a

1 whole. So elements of this assessment include
2 understanding the effect of the modified risk
3 information on tobacco use behaviors, what those
4 behaviors -- what do we anticipate those
5 behaviors being, and within particular tobacco
6 user groups.

7 So what is the potential impact of
8 modified risk information on use behavior among
9 current smokers? For example, what is the
10 potential impact on youth? How inherently
11 harmful is the product? And what are the changes
12 that we anticipate in these different groups in
13 health risks, based on tobacco use behaviors and
14 the toxicity or the harmfulness of the product?
15 And FDA would issue a marketing order when the
16 evidence supports a public health benefit.

17 The Federal Food, Drug, and Cosmetic
18 Act also requires companies that receive a risk
19 modification or exposure modification order to
20 conduct post-market surveillance and studies, and
21 this is described in the draft guidance available
22 for public comment.

1 For the last part of this
2 presentation, I want to highlight areas where
3 there may be room for clarification about our
4 expectations, and thus, room for improvement in
5 the submissions we receive.

6 Given the size and scope of these
7 applications, it's important to reiterate that
8 the organization of a submission is critical to
9 facilitating FDA's review. And the draft
10 guidance available for public comment, FDA
11 proposes inclusion of the following.

12 The cover letter, with the information
13 laid out here, a comprehensive table of contents,
14 a summary of the application which provides
15 enough detail to provide reviewers the general
16 understanding of what's included, and in
17 addition, a tabulated index of all studies and
18 analyses, organized by study type, with
19 hyperlink, with hyper-text link to each study and
20 analysis.

21 The application sections that have
22 been proposed include descriptive information,

1 label, labeling, and advertising, the
2 environmental impact, summary of all research
3 findings, a detailed section for scientific
4 studies and analyses, as well as a post-market
5 surveillance and studies plan.

6 One feature of the MRTPA pathway, and
7 one reason these submissions tend to be so large
8 is the requirement set forth in Section 911(b)(5)
9 regarding all documents, which states that MRTPA
10 applications must include all documents,
11 including underlying scientific information
12 relating to research findings conducted,
13 supported, or possessed by the tobacco product
14 manufacturer relating to the effect of the
15 product on tobacco-related disease and health-
16 related conditions, including information both
17 favorable and unfavorable to the ability of the
18 product to reduce risk or exposure, and relating
19 to human health.

20 I want to spend some time describing
21 FDA's interpretation of this requirement, as this
22 is an area that may benefit from greater clarity

1 in terms of what we mean by all documents.

2 First, in terms of the topical scope,
3 this includes studies relating to the effect of
4 the proposed product on tobacco-related diseases
5 and health-related conditions. Some examples
6 include studies conducted on the product itself,
7 or components of the product, such as testing for
8 HPHCs. Studies conducted with users of the
9 product, which may include market research,
10 consumer insight research, consumer perception
11 studies, and those related to population effects,
12 and clinical studies with the product or related
13 products.

14 As stated in the draft guidance, if
15 any of this information is not available, it is
16 useful for applicants to provide an explanation
17 for the omission. Oops. To be more specific,
18 let's discuss examples of types of study
19 documents.

20 First, for all of these studies, there
21 are examples of what we expect to be included.
22 This includes things like study reports,

1 protocols, investigator instructions, analyzable
2 data sets, including a description of how the raw
3 data were converted to an analyzable data set.

4 Things like study instruments,
5 statistical analysis plans, if used, programming
6 code, full copies of published articles and
7 reference materials, and individual case report
8 forms related to, in particular, participant
9 deaths, serious and unexpected adverse
10 experiences, and withdrawals where the
11 participant was exposed to the proposed modified
12 risk product.

13 Examples of what not to include,
14 include: cover documents or emails that merely
15 describe the transmission of scientific
16 information, case report forms from clinical
17 studies, except those that I just mentioned.

18 So this is one area of clarification
19 that we've communicated to the industry through
20 meetings and letters, is that we do not want to
21 receive every case report form for every
22 individual in your studies, but specifically

1 those listed in the -- in the first column.

2 Raw, unprocessed data is an example of
3 what else not to include. So for example, raw
4 chromatograms arising from analytical chemistry
5 testing. It's important to note that even though
6 some of these documents we're not going to be
7 requiring upon filing, may be, FDA may ask an
8 applicant to submit them upon request, and it's
9 FDA's expectation that any underlying information
10 will still be available for review during
11 inspections of clinical and/or non-clinical study
12 sites.

13 So in its review of MRTPAs, FDA has
14 noted the following types of missing documents.
15 Full descriptions of quantitative method
16 procedures, including method validation
17 information for HPHC testing methods, study
18 protocols, focus group study protocols, study
19 reports, underlying data sets, statistical
20 programs, and programming code use.

21 So these are just some examples of
22 types of documents that we've found to be missing

1 upon submission. It's also critical that, to
2 facilitate FDA's review of the labels for the
3 proposed modified risk product, it's helpful to
4 include copies of all labels for all products,
5 including the MRTPAs that reflect the actual size
6 and color proposed, as well as images of the
7 labels that provide a view of the full label, and
8 here's an example.

9 I want to reiterate the point that Dr.
10 Murphy made in her previous presentation, that
11 it's really critical for us that, if different
12 versions of the product have been tested, that
13 applicants clearly identify those different
14 versions across the application. For example,
15 what's really useful is to clearly identify and
16 explain differences, if there are differences, in
17 brand name.

18 For example, if a proposed product was
19 marketed differently in other non-US markets, and
20 thoroughly describing differences in product
21 versions, including if how the product differed
22 from the proposed MRTP. That is really valuable

1 for us to facilitate a timely review of the
2 evidence provided.

3 I also want to reiterate the point
4 that Dr. Murphy made about bridging across
5 products. In the context of MRTPAs, these
6 applications may include a variety of evidence.
7 This ranges from product-specific studies of the
8 proposed MRTPAs to epidemiological studies that
9 typically report disease risks for whole product
10 categories, for example, smokeless tobacco.

11 As we've communicated previously, if
12 applicants provide data from only a subset of the
13 products under review, for example, studies only
14 include selected sizes or flavors, or from a
15 whole class or category of products, it's really
16 helpful to provide bridging data, or a scientific
17 rationale for why the findings are relevant to
18 the products under review. This is a really
19 important piece.

20 As I mentioned, FDA is required to
21 make applications public. The draft guidance
22 available for public comment provides information

1 about that, but I wanted to communicate that
2 applicants, in order to facilitate our timely
3 review and posting of the applications, that
4 applicants consider the following for proposed
5 redactions.

6 Marking proposed redactions in the
7 text so that the text remains legible. So for
8 example, placing a box around the content,
9 submitting an index that lists the location of
10 each proposed redaction by page number, including
11 a statement explaining how the content of each
12 proposed redaction qualifies as trade secret or
13 commercially confidential information, and a
14 description of the competitive harm that would
15 result from disclosure. Having this more
16 detailed information just facilitates, as I
17 mentioned, more timely review and posting of the
18 applications.

19 As described in the draft guidance, as
20 Dr. Murphy mentioned in the context of PMTAs,
21 some of the data that may be used to support an
22 application include analysis of public use data

1 sets, or federal restricted use data sets.

2 Even though these data sets may be
3 publicly available, it's helpful for FDA to have
4 the exact data set that was used by the applicant
5 in order to understand what was done, and be able
6 to replicate the findings, as appropriate.
7 That's just another issue to consider.

8 And then, finally, I wanted to go back
9 to the topic of TPSAC meetings. As I've
10 mentioned, FDA has held three TPSAC meetings on
11 specific modified risk tobacco product
12 applications, and as we proceed, we're working to
13 apply what we learn to maximize the efficiency
14 and productivity of the TPSAC meeting.

15 So for example, our goal, as we
16 continue, is to focus the scope of the meeting to
17 the select scientific issues from the
18 applications, the ones that we deem to be the
19 most critical in making a determination, or that
20 we need the Committee to weigh in on.

21 Producing focused FDA background
22 materials for the Committee, streamlining the

1 presentation so there's more time for discussion,
2 crafting clear, focused questions for the
3 Committee to facilitate the most useful
4 discussion amongst the experts, and bringing in
5 additional subject matter expertise as needed to
6 provide the topic-specific expertise that would
7 be informative in the context of the particular
8 questions, in the particular application under
9 review.

10 So with that, I've gotten to the end
11 of my talk. I thank you for your time and
12 attention.

13 MS. RUDOLPH: I invite the panelists
14 to come join us up here at the front. So as the
15 panelists get settled in, I'll just remind
16 everybody here that we're giving all of the
17 outside speakers an opportunity to speak to us
18 about their observations, perceptions, and
19 whatnot about the presentations given in this
20 session. Each of them will be provided five
21 minutes, and we'll be trying to stick to that,
22 especially because following this panel, we'll

1 head into lunch.

2 So let's make this a robust,
3 interesting conversation, and once we get some
4 tech check here, then we'll move on with the
5 introduction. Are we all set? Okay, great. So,
6 Debbie, thank you.

7 MS. HAYDEN: Hi, I'm Debbie Hayden,
8 the Director for Product Development with Swedish
9 Match. I've been there a little over 30 years,
10 and I would like to thank FDA for this
11 opportunity to talk about PMTAs, and the MRTF
12 process.

13 Swedish Match has been very fortunate
14 to have gotten the PMTA all the way to the, to
15 the finish line, and it's a, it's a unique
16 position to be in. And I'd also like to thank
17 the panel before us with the SEs, because I
18 thought that was some very relevant discussion,
19 and it pertains directly to the content that goes
20 into the PMTAs.

21 To be honest, my experience is mostly
22 with the SE process, as I'm sure many of yours

1 is, and how that SE information is relevant is
2 you'll see a lot of overlap in the content
3 required in the PMTAs for the specific
4 information. So you're not going to have to, of
5 course, compare anything to a predicate. You get
6 to compare it to basically the population, and
7 that makes it also relevant to the research,
8 because the types of research that I've seen
9 being increasingly needed in the SE forum are
10 similar to those that you're, that we would find
11 needed in a PMTA setting.

12 So rather than limiting it to that
13 single predicate, now you're looking at that
14 research on a, in a broader scope. And so, along
15 with that relevance also comes with some of the
16 limitations that we have found in published
17 research for a lot of the products.

18 The smokeless products, there's kind
19 of a dearth of information out there for things
20 like the dissolution studies, and what should the
21 type of study be, and how should it be managed.
22 Things like exposure estimates.

1 There's inconsistency, even in the
2 published literature about what the daily use
3 amount to be, and that's kind of a basic need.
4 So it would be helpful to have some standards for
5 evaluation laid out in some of the guidances with
6 more detail.

7 For when you do get a PMTA approved,
8 and I'm sure many of you will, the work doesn't
9 stop there. As the guidance informs, you've got
10 post-market work to do, and that's, that
11 continues to take from your resources of people
12 used to work on applications, respond to the
13 questions from FDA, and it goes across the
14 organization. It's not one department.

15 So you're still looking for the annual
16 information on deviations for the products, the
17 published research that's relative to your
18 products, any adverse or seriously adverse
19 events. And the FDA takes those seriously, looks
20 at them to see if you're, you know, still
21 appropriate for your PMTA order, and they often
22 come back with a lot of very detailed questions

1 for, in particular, things like the research that
2 you've either done yourself, or that you've
3 located.

4 So good luck to everybody with their
5 processes, and I think I'll end my five minutes.

6 MS. RUDOLPH: Thank you so much. You
7 only used three and a half minutes, actually.
8 Matt, and you get your time now. Thank you.

9 MR. MYERS: Thank you. I'm Matt Myers
10 with the Campaign for Tobacco-Free Kids.
11 Obviously I bring a slightly different
12 perspective.

13 So I'm probably the first person who's
14 going to say I think FDA has done a first rate
15 job with the guidances that you've -- I think FDA
16 has done a first rate job with the guidances that
17 you've provided up to this point in time.

18 It would be great if they were rules,
19 but I think they have been detailed, they have
20 been specific, and they have reflected the fact
21 that regulation of tobacco is different than many
22 of the other subjects that you do.

1 The products that you're regulating,
2 by and large, kill people. So that your goal
3 here is to protect the public health, which
4 means, for the first time in history, you take a
5 very fresh look, and to provide new levels of
6 science and new levels of analysis.

7 I understand why the industry, which
8 has never been regulated before, is frothing
9 under the bit on it, but nonetheless, this is a
10 transformational time, and I think you have done
11 a first rate job in identifying things.

12 Second, both during the presentation,
13 then in the panel discussion before, I heard
14 concerns expressed about the need to look at
15 individual products. I don't think there is any
16 substitute for it, so I want to say on behalf of
17 public health, I think the type of individual
18 information about individual products you are
19 requesting is absolutely essential.

20 It's essential, not only to analyze
21 these particular products, but because there is
22 no other way for us to develop the base of

1 information needed for you eventually to be able
2 to do broader standards. If we don't really
3 understand the individual products in a way we
4 never have before, there is no way in the world
5 that you will be able to identify broader
6 standards to apply to a broader range of products
7 with any sort of meaningfulness.

8 We've seen this before. We've talked
9 about flavorings, and we've seen that flavorings,
10 heated at different temperatures, produce
11 different levels of toxicity. We heard it
12 earlier in the panel where you put paper onto
13 different products in order to reduce fire
14 hazards, and it causes certain levels of toxicity
15 that weren't anticipated.

16 The goal of regulation is for us to be
17 able to anticipate this, for the American public
18 no longer to be human guinea pigs on these sorts
19 of things. So I think you can't step back from
20 the individual requests that you're making. You
21 can't step back from the individual questions
22 that you're asking.

1 I think the same is true very much so
2 as you're looking at ENDS, because what we have
3 learned very much so is that we are in the early
4 stages of learning about these products, and we
5 can't make predictions without the kind of
6 information that you're talking about.

7 Recent studies have demonstrated that
8 different ENDS, when used differently, can reduce
9 the likelihood of quitting, as, and some might
10 increase the risk. We need to know which of
11 those are, and we won't know it without you
12 requesting the kind of information that's there,
13 including consumer use data.

14 We all talk broadly, but the only way
15 we will know whether or not any of these products
16 actually increase the risk of quitting, and under
17 what circumstances, and at what temperature, and
18 in what manner of use, is if you require that
19 data to come in, and it's consistent with what
20 you do on all other areas.

21 One area that I would suggest that we
22 disagree with is your statement that you don't

1 need, you don't require youth data. There is no
2 way for you to analyze whether or not these
3 products have an undue appeal to kids without
4 requiring youth data.

5 So the question shouldn't be whether
6 you do it, but how you go about it, and how you
7 require it in a way that is ethical and
8 appropriate, and doesn't lead to certain
9 problems. So I would encourage you to take a
10 very close look at that.

11 There's no way for you to evaluate
12 MRTTP of some of the products that are coming to
13 the market unless you understand youth perception
14 directly, youth appeal directly, and you require
15 the kind of studies that are needed to do that.

16 Fourth, I would also encourage,
17 because it hasn't been discussed very much, you
18 correctly said, and we would encourage this be
19 done even more, that information be done on
20 labeling and marketing. We know that marketing
21 influences who will use these products, how they
22 will use these products, and it will directly

1 impact public health. So it's not just what the
2 label claim is.

3 Unless you see the kind of marketing
4 that's there, we have recently seen the social
5 media marketing with images of some products that
6 are claimed to be less hazardous, that have
7 helped turn these products into a broad appeal
8 for kids across the country.

9 Then, the last critical point I want
10 to make is there is a fundamental difference in
11 the transparency of MRTP applications and PMTA
12 applications. The way MRTP applications have
13 been reviewed, there is public transparency.
14 There is an opportunity. That's not the case for
15 PMTA.

16 The use of, the manner in which MRTP
17 applications has been done demonstrates that it
18 is possible for public transparency of the
19 process, without giving away trade secrets. I
20 think that's absolutely essential for people to
21 be able to comment effectively, not just
22 industry, on how you handle PMTAs.

1 MS. RUDOLPH: Thank you, Matt.

2 Elaine?

3 MS. ROUND: Hello. My name is Elaine
4 Round. I'm a senior director in scientific and
5 regulatory affairs at REI Services Company, and
6 I'd like to thank FDA for hosting the workshop.
7 I think it's been a great discussion so far, and
8 I appreciate the opportunity to participate.

9 As for my experience, I've been at
10 Reynolds for 10 years, and the last 2 of which,
11 I've worked directly on regulatory applications,
12 and the 8 before that in the area of clinical
13 studies. And those clinical studies were
14 basically done to assess the potential for use
15 exposure and risk of tobacco products, such as
16 snus and e-cigarettes.

17 In my current role, I lead a group of
18 scientists and regulatory experts whose
19 preliminary responsibility is developing
20 regulatory submissions for new tobacco, new
21 cigarette products, which includes both
22 noncombustible and combustible cigarettes.

1 These applications include MRTPAs,
2 PMTAs, regular SEs, and exemption requests, and I
3 recently also had the opportunity to be a part of
4 the team who participated in the TPSAC process
5 for the Camel Snus MRTPAs.

6 So given that, my focus, well, that
7 and, in addition, prior to my current role, I led
8 a team to put together the scientific testing
9 strategy for the PMTAs on the ENDS products
10 produced by R.J. Reynolds Vapor Company that were
11 in the market as of August 8, 2016.

12 So given that much of my focus over
13 the last couple of years has been on PMTAs and
14 MRTPAs, I'll tell you that in my experience, the
15 draft guidances, all three of them, have been my
16 go-to. So they are very much a part of my
17 personal daily working life, and one of the
18 positive things I can say about those is that
19 they do have a lot of information in them, and I
20 certainly appreciate that.

21 But also, a challenge of them is that
22 they have a lot of information in them, and so

1 it's, it is challenging to use those to shape the
2 thinking of how to develop an application that is
3 focused, gives FDA the information that they
4 need, but also would allow getting products that
5 potentially are beneficial and/or appropriate for
6 the protection of public health out to the
7 public, and the information to communicate with
8 those, out to the public in a reasonable amount
9 of time.

10 So I will, I will say that I really
11 appreciated the presentations this morning. I
12 think a lot of the things I was going to say
13 actually were addressed. So one of the things
14 being that the process, in comparison to the SE
15 process, this is, these both are pretty young.
16 And they move a lot slower, and so kind of
17 gathering these learnings is a lot, I think, more
18 difficult on both sides of the aisle.

19 And so thank you for giving kind of
20 that summary of the learnings that you all have
21 gotten to date, and that's something that I'm
22 sure that our organization will certainly use.

1 So given that, I do hope that you'll
2 continue to do that on a regular basis, because,
3 you know, I know as we've gone through, at least
4 the Camel Snus process, and I'm sure others have
5 gone through the process, that we've learned
6 along the way, I know there's things that we've
7 learned on, in documents that maybe aren't
8 publicly released, that I hope that you'll
9 continue to amass that information.

10 Some very specific things include that
11 concept of all documents that I know Dr. Apelberg
12 just brought up. That's been a difficult thing
13 for us in terms of, especially products that have
14 been on the market in the past, there's a lot of
15 data. There's a lot of things that need to be
16 included there.

17 And so we want to give FDA everything
18 that they're looking for, but on the other hand,
19 I know that you can get really bogged down in the
20 review process as well. So some clear boundaries
21 around how to include that, and what to include.
22 Maybe some clear boundaries would be, would be

1 helpful.

2 In addition to that, the concept of
3 bridging, I'm glad that came up again today as
4 well. I think that's a really important concept.
5 And again, having an example that FDA has
6 accepted, of a very specific use of bridging
7 would be helpful to us to understand how to
8 better use that.

9 And then, in addition, one other
10 thing, it's mentioned in the MRTPA, in the Act,
11 and in the draft guidance, how consumers are
12 actually using the product. And I know there's
13 an actual use section of the MRTPA draft
14 guidance, but some more information around what
15 you're looking for on actual use timing,
16 especially for products that aren't in the market
17 yet.

18 How do we assess that in a way that
19 the FDA can better assess the applications? How
20 many, how many people? How many, how long, would
21 be really helpful.

22 And then, you know, getting a little

1 bit bogged down in details, but I do want to come
2 back to, and not lose sight of the fact that the
3 goal of the pathways is really to give consumers
4 access to products that are appropriate for the
5 protection of public health benefit, potentially
6 benefit public health, and give people the
7 information and the communication that is correct
8 for assessing risk.

9 And so we want to give the data that
10 we need, but I also want to make sure, you know,
11 there's not going to be a perfect data set, so
12 how do we come to that middle ground and get
13 things out, knowing that there is a robust post-
14 market surveillance process that can be taken
15 advantage of in the future? Thank you.

16 MS. RUDOLPH: Thank you, Elaine.

17 Mohamadi?

18 MR. SARKAR: Thank you. First of all,
19 I want to thank CTP for inviting me to
20 participate on this panel, and I also want to
21 thank Dr. Murphy and Dr. Apelberg for giving this
22 presentation. That was very helpful to get some

1 clarifications on many of the issues that have
2 been on top of our mind.

3 I am a fellow at Altria Client
4 Services, and in my role, I provide strategic
5 direction on developing the scientific evidence
6 for regulatory submissions. And today, I'm going
7 to share our perspective, based on our
8 experiences of filing both a PMTA and an MRTPA.

9 You know, these discussions have been
10 very helpful, and we hope that, you know, FDA
11 kind of uses this platform continuously, and
12 continues to build on it for future reference as
13 well.

14 At the offset, I want to just agree
15 and totally support the commitment that FDA has
16 made to establish these rules of the road for
17 PMTAs and MRTPAs. We need clarity on many of the
18 topics Dr. Murphy mentioned, appropriate for the
19 protection of public health. We need some more
20 clarity as these foundational rules are being
21 established.

22 Also, around the standard of the

1 scientific evidence that would be necessary for
2 regulatory decisions is an important thing to
3 consider as these rules are being established.

4 The foundational rules should also
5 clarify many topics like post-market
6 surveillance, population modeling, abuse
7 liability, for example, and last, but not the
8 least, I think it would be useful for us to get
9 specific and clear direction from FDA regarding
10 its expectation on the scientific evidence for
11 likelihood of use in non-users, particularly
12 youth.

13 I also want to use this opportunity to
14 give you some specific examples of considerations
15 that FDA may want to keep in mind, and then I'm
16 going to offer some practical solutions for that.

17 My first one is that FDA should
18 consider establishing an accelerated PMTA
19 pathway. Today, it takes several years to
20 generate the evidence in support of a PMTA. And
21 even then, we don't know whether that evidence is
22 sufficient enough.

1 You know, FDA could look at other
2 centers, for example, that abbreviated new drug
3 application. At CDER is very well-established.
4 Similarly, there is an accelerated approval, a
5 fast track or priority review pathway that exists
6 with the agency.

7 You know, the priority review pathway
8 is used in CDRH, where applicants can submit
9 supplements to a previously approved application,
10 and if that, if that product is slightly
11 modified, or if there's an improvement made in
12 the product, then that just builds on the
13 previously approved product. CTP could consider
14 similar approach for authorized products.

15 The second point I want to make is
16 around the evidence for impact on population.
17 Now, the impact on the population, and Dr.
18 Apelberg point out, you know, this is kind of the
19 population as a whole, including users and non-
20 users, and that's very difficult to predict in a
21 pre-market setting.

22 You know, we think that such evidence

1 is best generated in a post-market setting under
2 real world conditions. You know, we urge FDA to
3 look at CDRH and CBER, which recently published a
4 guidance on real world evidence.

5 In fact, these centers rely on post-
6 market evidence for regulatory decisions, and it
7 gives them some flexibility to assess the actual
8 use of the product under real world conditions
9 that's optimal.

10 The third point that I want to make is
11 around the evidence that is needed for
12 substantiation of a modified risk claim. Once
13 again, Dr. Apelberg had some interesting points,
14 but I think we had remembered that for some of
15 the newer categories like heat not burn or e-
16 vapor, epidemiological data is not going to be
17 available.

18 And today, we have many methods that
19 are based on sound scientific principles, for
20 example, as Dr. Apelberg pointed out, in non-
21 clinical studies with in vitro and in vivo
22 studies, randomized clinical trials, switching

1 studies with biomarkers of exposure and
2 biomarkers of potential harm, quality of life
3 assessments.

4 The totality of the evidence, if all
5 of these data points converge, then that should
6 allow us to infer a reduction in a disease risk,
7 and we urge FDA to consider developing a
8 biomarker qualification program that exists in
9 CDER, where the agency works with industry and
10 academia to qualify biomarkers for specific
11 regulatory decisions.

12 I see my time is up, so I just want to
13 end, I just want to end by saying that, you know,
14 I hope that this discussion helps FDA realize,
15 set a foundation of rules that are practical,
16 they're viable, and pragmatic pathways for PMTAs
17 and MRTPAs. Thank you.

18 MS. RUDOLPH: Thank you. Would you
19 all like to introduce yourselves too, again?

20 MR. APELBERG: Hi. Ben Apfelberg,
21 Director of the Division of Population Health
22 Science.

1 MS. CALLAHAN-LYON: Priscilla
2 Callahan. I'm the Deputy Director for the
3 Division of Individual Health Science.

4 MS. RUDOLPH: Great. So before we get
5 started, we did get a nice number of questions
6 from the audience, both online and in the room.
7 We have 20 minutes together, so that will take us
8 up to about 12:30, before we depart for lunch,
9 just so you all have a sense of expectation. And
10 if we're enjoying ourselves, maybe we'll go a
11 couple extra minutes. We'll have to see.

12 But to begin the conversation, it was
13 brought to my attention, it might be really
14 important to highlight or to remind people in the
15 room that CTP does not approve tobacco products.

16 We authorize new tobacco products to
17 be marketed in the United States. So just kind
18 of keep that in mind as we continue to move
19 forward, in case that's not clear. So for, and
20 I'm just going to put the questions out.

21 More than likely, actually even before
22 I do that, let me ask Ben and Priscilla, based on

1 what you heard from our panelists, are there some
2 topics that you would, right off the bat, like to
3 address that were raised?

4 MR. APELBERG: Yes. You know, I mean,
5 I think, I guess I took some notes while these
6 guys were talking. I mean, some of the points
7 that were raised about, you know, all documents,
8 that Dr. Round talked about bridging, actual use,
9 you know, we, I guess I just wanted to point out
10 that we do recognize the challenge, you know,
11 with respect to some of these issues, with
12 respect to the all documents requirements.

13 You know, we are, as I mentioned in my
14 presentation, you know, we are very much learning
15 from the experiences that we've had to date with,
16 you know, just a few applications, but in terms
17 of what really is necessary and critical for
18 substantive scientific review, and what might be
19 less so, and therefore, not necessarily needed
20 upon filing. And so we look to be able to
21 continue to communicate that.

22 I, you know, I flagged a few things.

1 I guess I also wanted to touch base on what Dr.
2 Sarkar mentioned about the challenges of studying
3 likelihood of use, you know, in a pre-market
4 context, and it's, I mean, for sure, it's
5 definitely true that that's a challenge.

6 You know, and that's the challenge
7 though that we face, you know, and what I think
8 we've tried to lay out is the ability to really
9 tie together multiple lines of evidence to try to
10 draw the most sound inferences we can.

11 I mean, we can't know for certain
12 what's going to happen in the world, you know,
13 once an order is issued, but we do have
14 experiences from other countries, and we do have
15 ways to study the potential appeal of products,
16 both to current users, to non-users.

17 You know, in the context of MRTPA,
18 obviously a key aspect then is what is the impact
19 of them communicating that modified risk
20 information, and you know, I think we've seen
21 studies that have come in that have been useful
22 in helping to address that, but even in that

1 case, we recognize that that's in a controlled
2 setting. It might be a onetime exposure. It's
3 not necessarily the environment that's going to
4 be, you know, seen if a product is marketed
5 widely, and for a long period of time.

6 So not really answers to those
7 questions, but more a recognition of some of the
8 challenges, that we understand those as well.

9 MS. RUDOLPH: Thank you.

10 MS. CALLAHAN-LYON: And I'll just
11 comment about the, comment about the accelerated
12 PMTA pathway. That would be certainly something
13 for us to consider. I don't think we have the
14 level of experience at this point in time to do
15 that, so, so noted.

16 QUESTIONS AND ANSWERS

17 MS. RUDOLPH: Thank you. So to head
18 into our questions here, the first one is, if a
19 proposed PMTA new product is in an established
20 product category, for instance, moist snuff
21 tobacco, and does not deviate from that category,
22 is new product-specific research necessary? And

1 it further goes on, what types of external
2 scientific research would be sufficient? Does
3 FDA have recommendations for how to avoid gaps
4 for this scenario?

5 MS. CALLAHAN-LYON: Well, in the PMTA
6 context, if you've got a product that's in a
7 previously established product category, and
8 you're trying to get an authorization for your
9 product as appropriate for the protection of
10 public health, then you need to demonstrate why
11 that product is appropriate for protection of
12 public health, as compared to other products in
13 that category.

14 So you would need to be, if you've got
15 that information without doing additional
16 studies, then give us the information. If you
17 don't, then you may have to do studies, and it's
18 really going to be case by case, depending on
19 what exactly you're trying to accomplish, and how
20 you're trying to market the product.

21 MS. RUDOLPH: Okay. Thank you. And
22 as a follow-up to that, another question asked

1 here is, can an approved PMTA product be used as
2 a predicate product for an SE application?

3 MS. CALLAHAN-LYON: I'm not an expert
4 on SE, but my friends on the front row are
5 shaking their heads no.

6 MS. RUDOLPH: Okay. There we go.
7 Thank you. So going to the bridging, a question
8 came forward, can you comment on bridging with
9 respect to, for example, HPHC testing? Some
10 product categories have thousands of SKUs, and
11 numerous permutations. This combined with time
12 and laboratory constraints make testing all
13 products infeasible by application deadlines.

14 MS. CALLAHAN-LYON: Okay, I think Dr.
15 Murphy addressed this to some degree in her
16 presentation when she was talking about giving us
17 things at both the top, the bottom, and maybe in
18 the middle, so that we cover the range, and
19 that's the kind of information where bridging
20 could be potentially helpful, depending on what
21 you're testing.

22 So if it's a product chemistry

1 testing, something at the top of the line, the
2 bottom of the line, and somewhere in the middle.
3 Same thing for temperatures or controls, other
4 ingredients, HPHCs, any of those informations you
5 can bridge from the top and the bottom and the
6 middle.

7 MS. RUDOLPH: Okay, thank you. I'm
8 going to continue on with our questions then
9 here. So here's another one to the FDA. In the
10 case of an MRTPA, is -- wait.

11 In the case an MRTPA is authorized,
12 what involvement does FDA expect to have in the
13 post-market surveillance plan? Will they
14 implement their own surveillance, and/or will
15 they work with the applicant on this? Do they
16 have some initial thoughts on what they would
17 expect a surveillance plan to look like?

18 MR. APELBERG: Yes, so you know, as I
19 mentioned, post-market surveillance in studies is
20 a specific requirement of the MRTPA pathway if an
21 order is issued, and you know, our expectation I
22 think would be that, you know, in the case that,

1 when the first MRTPA order is issued, and we
2 would work with the company to ensure that
3 there's detailed protocols that are developed
4 that would address the key considerations that
5 are laid out in statute, as well as the, you
6 know, any particular issues that are raised in
7 the context of review that, you know, for
8 particular attention.

9 I think, in some respects, it, you
10 know, it depends on the nature of the
11 application, like, where, you know, if you have
12 an established product, where the health risks
13 are pretty, you know, have been studied for
14 decades, that's one, you know, scenario.

15 Another scenario may be a completely
16 new product where we have, you know, confidence
17 that, some degree of confidence in the risks, but
18 you know, there may be more research that needs
19 to be done.

20 I will say that one of the, you know,
21 one of the key aspects that we've talked about,
22 you know, both in the reviews, as well as in the

1 TPSAC discussions, is understanding how people
2 use the product. So there's the behavioral
3 aspect of surveillance that's going to be
4 critical.

5 There's some unique considerations, I
6 think, too, that'll have to be discussed when
7 you're talking about surveillance of a particular
8 specific product, you know, a brand and a sub-
9 brand of a product that's different from the
10 national surveillance that we typically do, so
11 there will have to be different considerations
12 for how you identify users, potential users,
13 follow them over time to assess that.

14 But you know, really the calculation,
15 you know, in the end, comes down to how, you
16 know, what do we know about the risks of these
17 products, and who stands to benefit and who may
18 be harmed by it, and therefore, are we seeing the
19 behavioral patterns that indicate a benefit --

20 MS. RUDOLPH: Thank you.

21 MR. APELBERG: -- you know,
22 specifically, that, you know, for example,

1 smokers are completely switching, that we're not
2 getting much uptake among youth, among previous
3 non-users. I mean, those are important aspects.
4 But --

5 MS. RUDOLPH: Yes.

6 MR. APELBERG: -- so there's that work
7 that will go on, and then of course, within CTP,
8 I mean, we do have our own research and
9 monitoring efforts that we of course use to
10 understand what's happening, you know, in the, in
11 the US, in terms of tobacco use and its impacts,
12 that we would also continue to be doing that as
13 well.

14 MS. RUDOLPH: Great. And I see that
15 Matt has a comment here.

16 MR. MYERS: Yes. I just, I want to
17 make sure that we don't confuse that post-market
18 surveillance is not a substitute, particularly
19 for really good data, particularly with regard to
20 prediction of who is going to use a product, and
21 under what circumstances, and what the population
22 effect will be with regard to that. And all of

1 our tools for measuring post-market surveillance
2 are slow.

3 And so, you know, we could well be in
4 a, in a position where we're having a public
5 health disaster if we don't require very rigorous
6 pre-market data on public perception, marketing,
7 how we project the product will be used, and
8 requiring the manufacturer to have data that's a
9 lot faster than this survey data that we have
10 here.

11 So I just think it's important to
12 understand that pre versus post, in this setting,
13 raises certain other issues so that post-market
14 surveillance makes sense, but not as a
15 substitute.

16 MS. RUDOLPH: And that leads to our
17 next question, which is, what are really some of
18 the specific challenges to obtaining population
19 data in pre-market settings?

20 MR. APELBERG: In -- oh, is this for
21 us, or for the --

22 MS. RUDOLPH: It's for whoever --

1 MR. APELBERG: -- for the industry?

2 MS. RUDOLPH: -- wants to take it.

3 Jump in, whoever --

4 MR. APELBERG: Maybe the industry
5 should --

6 MS. RUDOLPH: -- wants to go.

7 MR. SARKAR: Well, so I'll take a stab
8 at it and see --

9 MS. RUDOLPH: Okay, thank you,
10 Mohamadi.

11 MR. SARKAR: -- if others want to
12 chime in. You know, a lot of conversation has
13 been going back and forth, so I just want to
14 maybe anchor some points for discussion. I don't
15 think that, you know, we're saying that, you
16 know, not to generate any pre-market evidence.

17 The point I was trying to make is that
18 it's difficult to predict what's going to happen
19 in the real world in a pre-market setting,
20 particularly for a new product, and I totally
21 agree with Dr. Apelberg that, you know, even with
22 the post-market, you know, it takes a while for

1 the product to penetrate into the market.

2 But nonetheless, and I think it's
3 important to remember that if you have a product
4 that has a promise for harm reduction, you know,
5 let's not hoist the precaution and principles,
6 and keep those products from getting in the hands
7 of millions of smokers who are looking for
8 reduced risk alternatives, and I can totally
9 understand that then FDA is in a bind where you
10 have to make a decision to weigh the risks and
11 the benefits. So it is a difficult situation.

12 In terms of, you know, post-market
13 setting, one of the challenges that we face is
14 that with these large national surveys, you know,
15 there's a time lag before we get the data. And
16 also, you know, sufficiency of the sample size,
17 because it takes a while for the product to
18 penetrate into the marketplace.

19 And the other thing that, you know,
20 Dr. Apelberg mentioned about, you know, people
21 who completely switch, I think we had to also
22 remember that this switching process is going to

1 be gradual, because for some of these products,
2 you know, it's not instantaneous that, you know,
3 smoker will immediately switch. There will be a
4 phase of dual use that will eventually lead to
5 complete switching, because, you know, the smoker
6 has to adapt to this new behavior, depending on
7 the product.

8 MS. RUDOLPH: Thank you. Elaine or
9 Debbie, do you have any other comments on that,
10 with regards to your perspective as
11 manufacturers, with regards to challenges in
12 obtaining pre-market strategies, or settings,
13 rather? Population data and pre-market settings,
14 rather?

15 MS. ROUND: Yes, I guess I'll echo Dr.
16 Sarkar's comments in that, obviously, if the
17 product is not on the market, there are some big
18 challenges to getting that type of data. I will
19 say that there is, you know, there is survey
20 research that that can be done on consumer
21 perceptions, likelihoods of use.

22 The challenge there is, instead of

1 seeing if, for example, in the case of modified
2 risk, tobacco product application, instead of
3 continually seeing the modified risk information,
4 they see it once or maybe a couple of times, or
5 not as, not as robust as would be the case in the
6 market.

7 So in some, in some ways, you know,
8 you're not, you're not getting the full effect of
9 what you might get if that kind of information
10 was in the market. But you know, we have, we
11 have a whole group at Reynolds who does this
12 work, and we've conducted an algorithm to try to
13 take that likelihoods of use data and put into
14 population model to try to predict that.

15 So there are certainly challenges,
16 again. It's not really going to be until it's in
17 the marketplace, until we see the full effects of
18 those products.

19 MS. RUDOLPH: And Debbie?

20 MS. HAYDEN: And while I agree with
21 that, our experience with the Snus products was
22 that they had been in the market for decades.

1 We'd been making improvements for decades, and
2 I'm sure most of you've heard, you know, Swedish
3 experience, and that information still was
4 difficult to wrap your hands around to present to
5 FDA in a meaningful way.

6 And as you, as you note, we've even
7 had to come back and do amendments to the MRTP.
8 So it's not a perfect situation, even if the
9 product has been in the market.

10 MS. RUDOLPH: Okay. Matt?

11 MR. MYERS: Yes, I apologize for
12 jumping in.

13 MS. RUDOLPH: No, please.

14 MR. MYERS: But I do think we have to
15 recognize, we are in a different world, and FDA
16 needs broad regulations, because market
17 penetration can happen very rapidly.

18 We've just seen what happened with an
19 ENDS product with Juul, whereby it has swept the
20 nation of our nation's kids before we even knew
21 it had happened, by using marketing tools that
22 others had not seen, with a product that was

1 extraordinarily attractive.

2 So when we think about, there are some
3 products that will take a long time to penetrate.
4 There are other products that will sweep the
5 nation, and we need to make sure that FDA has
6 rules of the road in place that govern these
7 products before that takes place so we're not
8 always playing a Whack-A-Mole later on when it's
9 too late to put the horse back in the barn.

10 MS. RUDOLPH: Thank you. I'm going to
11 move onto another question here so we can try to
12 get to some more of these in our stack. Thank
13 you very much.

14 So this also relates to surveillance,
15 and someone had stated here that the statute does
16 not require post-market surveillance for 910
17 PMTAs. Is that correct? If so, then why does
18 FDA require post-market evidence for PMTAs?

19 MS. CALLAHAN-LYON: So you can't
20 require post-market studies. We can, however,
21 have things that we ask for applicants and those
22 that we grant authorization to submit to us in

1 terms of post-marketing reporting. So that's
2 allowed.

3 MS. RUDOLPH: Thank you. And this
4 probably is something that you could also answer,
5 Priscilla. How does CTP define protection of
6 public health in the PMTA context? Must
7 applicants demonstrate net public health benefit?
8 Or maybe this is Ben.

9 MR. APELBERG: Sorry.

10 MS. RUDOLPH: I was just trying to
11 help you out.

12 MS. CALLAHAN-LYON: How to define
13 public health benefit. That is a very tricky
14 question. I don't know that there is a specific
15 answer. I think our goal is to try to have
16 products that are available to current tobacco
17 users that are less dangerous than the products
18 that they are currently using, while at the same
19 time, protecting those that are current non-
20 tobacco users, and making it something that is
21 not going to be so appealing to them that we're
22 going to attract a market that we don't want to

1 attract.

2 Now, there is not a clear definition
3 of that, and I am hopeful that over time, as we
4 have new tobacco products out there, that we move
5 the calculation of what is appropriate for the
6 protection of public health. So what's
7 appropriate this week hopefully will not be
8 what's appropriate five years from now.

9 MS. RUDOLPH: Thank you. So we're
10 going to --

11 MS. CALLAHAN-LYON: Is that vague
12 enough?

13 MS. RUDOLPH: Yes. And we're going to
14 move in to a few questions about HPHCs, and if
15 Hans or Kim may be available to jump in, that
16 would be great.

17 So the first question here is, does
18 FDA consider the total mass of HPHCs equally, or
19 are certain HPHCs of particular interest?

20 MR. ROSENFELDT: So PMTA is a little
21 different because it's not like SE where you are
22 comparing to a predicate product. Here, we're

1 comparing to set of comparator products. And for
2 MRTP, it's even, you know, it's even more
3 complicated.

4 So I guess the answer is we consider
5 the totality of the HPHCs, and we look at what
6 was given to us, and you know, and we look to see
7 whether the HPHCs provided can cover the, give us
8 an understanding of the relative risk, you know,
9 in the case of PMTA, relative to the market, and
10 the users who are using the products that we
11 think, you know, are using the product. I hope
12 that answers the question.

13 MS. RUDOLPH: It looks like Kim has
14 some other additional thoughts.

15 MS. BENSON: Tag team. One other
16 thing that's good to remember when you're looking
17 at the HPHCs is, you know, they don't all have
18 the same target. They don't have the same
19 toxicity.

20 So just a case in point, if you have
21 a, you know, reduction in an HPHC that causes
22 cancer, and a huge increase in one that causes

1 cardiovascular toxicity, they're not going to
2 cancel each other out, right? So we've seen that
3 happen in applications, so I just wanted to alert
4 folks to keep that part in mind as well.

5 MS. RUDOLPH: You can stay close.
6 We've got a couple more HPHCs, but I guess you
7 guys could do rock paper scissors over there.

8 So our next one is for a closed system
9 ENDS product. Does FDA weigh HPHCs in e-liquid
10 and aerosols equally, or is there emphasis on one
11 or the other, which may get to your previous
12 comment, but --

13 MS. BENSON: Okay, so yes, this is
14 very different if you think about the fact that
15 there are, with ENDS, a lot of these things are
16 added, right?

17 It's not a product of an agricultural
18 product that you had no control over the soil it
19 was grown in and it's not a part of a combustion
20 or paralysis action. So you're going to know
21 exactly how much is in the liquid, right? It's
22 been added.

1 And so you could just use that and
2 say, this is how much it is, and justify the
3 level of the HPHC based in the fluid. Ultimately
4 though, it's what the user is exposed to, right?

5 So when we're looking at it, we really
6 would like to see it in the aerosol, but we
7 appreciate that if you already have added it, and
8 you want to just go by that number and save the
9 hassle of measuring it in the aerosol, you could
10 do that.

11 But know then that we'll just assume
12 100 percent, you know, based on what's in the,
13 you know, and one way you could address that is
14 by saying, well, there might be 100 percent in
15 the fluid, but in the aerosol, there's very
16 little, and here's the measurement there. So in
17 the end, it is all about what the user is exposed
18 to. So --

19 MS. RUDOLPH: I have one final one for
20 our tox folks. What guidance can FDA give on
21 selecting device hardware to use when generating
22 HPHC best data for e-liquids?

1 (Off microphone comments.)

2 MS. RUDOLPH: Oh, okay, come on up.
3 Oh, we'll pull you in from the wings too. Come
4 on.

5 MR. CECIL: There's no really good
6 answer for that. We know that HPHCs in the
7 aerosol change, depending upon the temperature of
8 the coil.

9 Obviously you want to be looking at
10 any device that may be likely to be, or that
11 could be used with your e-liquid, if you're
12 marketing an e-liquid product. If you're
13 marketing a combination device, where it's a
14 device and an e-liquid, well, it would make sense
15 to evaluate it with that product combination.

16 So I think you end up, in all
17 likelihood, looking at the worst case scenario
18 and the best case scenario in terms of hardware
19 for that comparison, and do a bracketing sort of
20 approach.

21 MS. RUDOLPH: So I asked if we could
22 have five more minutes, and I got the green

1 light, so we're going to be here for a few more
2 questions, folks.

3 So moving away from toxicity, and
4 moving on to another topic area, will the FDA
5 provide general direction on studies including
6 kids to demonstrate lack of interest in a PMTA
7 candidate product?

8 Does that make sense? I'm reading it.
9 I'm sorry. I'm just Vanna here. I can't
10 interpret. Did somebody write this question?

11 PARTICIPANT: What are you going to do
12 about youth data?

13 MS. RUDOLPH: Okay. There we go.
14 There's the bottom line. What are you going to
15 do about youth data, is the question.

16 MS. CALLAHAN-LYON: With respect to
17 the PMTA?

18 PARTICIPANT: Yes.

19 MS. CALLAHAN-LYON: Yes. Well, I
20 think we've been very clear that we don't expect
21 you to necessarily do studies in youth with
22 regards to PMTAs.

1 We would like to have some explanation
2 of how you think that youth are potentially able
3 to use the product, how they would be likely to
4 use the product, how they would get the product,
5 and any sort of extrapolation of data, either
6 from young adults, or from some of these other
7 population survey information that we have.

8 That's about the best I can tell you
9 at this point in time, and I'm sure that there's
10 other input over here, and I think Iilun also has
11 some comments.

12 MS. MURPHY: Thank you. I want to
13 make a clarification. So in my presentation, I
14 mentioned that youth behavioral data are not
15 required, and we don't have regulations right now
16 to state that youth behavioral data required.
17 However, clearly depending on the tobacco product
18 that is the subject of the PMTA, we may be very
19 interested in youth behavioral data.

20 So again, if we are to determine if a
21 product is appropriate for the protection of
22 public health, and we know there is an issue with

1 youth interest in that particular product, or
2 similar products, then I think it would be very
3 helpful for the applicant to address the issue.

4 Now, whether you conduct your own
5 studies specific to that product, or bridge from
6 existing studies that have looked at youth use
7 of, you know, such products, that's up to you.
8 But again, provide whatever justification and
9 rationale for addressing youth use, if that is
10 likely to be an issue for that specific product.

11 Now, I think in terms of perception
12 studies, there are, as discussed, general
13 principles that apply to developing perception
14 studies appeal, and actual use studies.

15 And then, especially when dealing with
16 youth, there are human subject protection issues
17 that have to be considered, and there are plenty
18 of guidances and regulations that pertain to
19 developing studies that involve youth. So I
20 think that those can be consulted.

21 So obviously human subject protection
22 is a big issue for that. We want to make sure,

1 if youth studies are done, that they're done
2 appropriately, and companies can come in to
3 discuss, if they're planning to conduct a youth
4 study, you know, I highly urge you to come into
5 CTP ahead of developing that study, and come to
6 talk to us about your plan and protocol
7 development.

8 Sorry. I want to just go back to one
9 more thing in terms of appropriate protection of
10 public health. I tried to address that in my
11 presentation, but basically, as Dr. Callahan-Lyon
12 was talking about, you know, really, the impact
13 on the morbidity and mortality, the current
14 status quo is not acceptable.

15 I think we all understand that 500,000
16 deaths a year is not okay. And the objective of
17 the PMTA is to shift the marketplace such that we
18 develop more products that have less harm to the
19 users who are not able to quit.

20 So you know, today, what is
21 appropriate for the protection of public health,
22 like Dr. Callahan-Lyon was saying, our standard

1 may be different, you know, five years from now,
2 as the marketplace shifts. So I hope that helps
3 kind of characterize what we're trying to
4 accomplish. Thank you.

5 MS. RUDOLPH: So this is for our FDA
6 colleagues here. What is CTP's criteria for
7 determining if a PMTA is sent to TPSAC or not?
8 And further, it goes on to state, what would be
9 the basis for CTP making such a request, and what
10 would CTP expect to gain from a TPSAC review?

11 MS. CALLAHAN-LYON: Okay. So as Dr.
12 Apelberg discussed, MRTPAs are required to go to
13 TPSAC. The PMTAs are not. We have not yet taken
14 a PMTA to TPSAC.

15 I think that probably the primary
16 indication would be is if we thought something,
17 from a scientific standpoint, would benefit from
18 discussion among the experts on the advisory
19 committee.

20 So it would probably be an extremely
21 focused, scientific discussion that would lead us
22 to bring a PMTA discussion to the advisory

1 committee.

2 MS. RUDOLPH: Thank you. If a granted
3 MRTPA or PMTA cannot be utilized as a predicate
4 in an SE application, does that also eliminate
5 the EX requirement -- do I have that right? --
6 for minor modifications of the tobacco product?
7 Okay.

8 (Off microphone comments.)

9 MS. RUDOLPH: Here we go. Thank you,
10 Marcella.

11 MS. DOLLING: So projects that are
12 eligible for the exemption request pathway are
13 products that are legally marketed. So a PMTA
14 would be eligible to receive an exemption request
15 under that pathway.

16 MS. RUDOLPH: Excellent. So for our
17 final question, although I do have a couple more,
18 but I'll take one, I'll just do one last one so
19 we can get to lunch here. So when and how would
20 I use an investigational tobacco product
21 application to support a PMTA or MRTPA?

22 MS. CALLAHAN-LYON: Okay. So an

1 investigational tobacco product request, at this
2 point in time, those are not applications, as
3 such. Those can be certainly used to support a
4 PMTA, and they actually have been used to support
5 PMTAs.

6 They, you can do the studies. Those
7 come in and FDA looks at the protocol, and we
8 look at the investigational product. We review
9 the protocol for the standpoint of human subject
10 protections.

11 This provides you an opportunity to
12 get feedback on the protocol, on the design, on
13 the study, and it's another way of gaining input
14 into your application and the things that you
15 might want to consider when you're making the
16 study design, and then you can use those as human
17 studies that would support your application down
18 the road.

19 MS. RUDOLPH: Thank you very much.
20 Any final comments? Okay, very good. Okay.
21 We'll end this session. Round of applause for
22 our panel. So as we head now into lunch, if you

1 all would plan to be back at a quarter til 2.

2 Thank you.

3 (Whereupon, the above-entitled matter
4 went off the record at 12:42 p.m. and resumed at
5 1:52 p.m.)

6 MR. HOLMAN: Okay. We're going to go
7 ahead and get started with our last session here.
8 I'm going to kick things off and then Eshael is
9 going to come up and run things for the rest of
10 the session.

11 But as I said yesterday, at the end of
12 the day, we're going to do this session a little
13 bit different because of the issue with not being
14 able to have our colleagues from the Office of
15 Compliance and Enforcement here. We still do
16 want to hear what you guys have to say.

17 Unlike the other sessions where there
18 was much more -- there was a discussion, a
19 conversation. This is really just going to be a
20 listening session for us. We are taking notes on
21 things. We're videotaping this so that we can
22 take back what we got from you guys during this

1 session back to our colleagues at Office
2 Compliance and Enforcement.

3 What we're going to do is start off
4 with -- our two panelist will share their
5 perspectives as manufacturers of deemed products,
6 but we also have a microphone set up here on the
7 stand that you're welcome to come up, and hope
8 that others will come up and share their
9 experiences, their perspectives, comments,
10 questions that they have to the microphone.

11 I will ask you as you come up to the
12 microphone, you will see the table there where
13 the transcriptionist is there is a notepad. If
14 you can write your name and affiliation for the
15 transcriber, and then when you step to the mic if
16 you can just repeat that so that he can
17 appropriately capture the transcription. All
18 right, with that I'll turn over to Eshael.

19 MS. JOHNSON: Thank you very much.
20 Welcome back from lunch. So welcome to our last
21 session of the day. Session 8. A little tweak,
22 still going to talk about newly deemed tobacco

1 products, and we can have our two panelists here,
2 same drill, five minutes. Tell us a little about
3 what you do and give us your statements.

4 MR. GRAHAM: Thank you. I'm looking
5 forward to this session. I think it's going to
6 be, I think much more interactive. I want to
7 encourage all of the colleagues. I'm looking
8 forward to this session. I think it's going to
9 be very interactive. I want to encourage all of
10 our colleagues, representatives from ENDS
11 companies and others to take the opportunity to
12 also share perspectives. So I'll try and keep
13 things brief from my point of view.

14 I want to start by thanking FDA for
15 organizing the meeting and for inviting me to
16 participate on a panel. By way of personal
17 introduction, my name is David Graham. I'm Chief
18 Impact Officer at NJOY. I started my career with
19 nicotine products in '92, 1992, working with
20 nicotine replacement therapy, medicinal products.

21 I work with Pfizer and Johnson &
22 Johnson globally in that capacity for around 20

1 years. And I grew, I should confess increasingly
2 of the view that nicotine replacement products
3 had well-efficacious and safe in the contexts of
4 considerable review in a medicinal context were
5 limited in their efficacy and reach of their
6 population level and the real impact that they
7 had the population.

8 I became increasingly interested in
9 the promise of electronic nicotine delivery
10 systems. And I joined -- I left the former
11 industry and joined NJOY in 2013. I work with
12 NJOY and during my time over the last five years
13 I also see over any e-liquid contract
14 manufacturing company with an analytical lab. I
15 lead a consulting firm by working with smaller
16 ENDS companies and preparing their programs for
17 PMTAs. And I'm back full-time at NJOY where I
18 oversee the work that we do in focusing in what I
19 believe is a very important responsibility to
20 recognize the importance of the determination of
21 impact, the impact of products such as ENDS.

22 And how FDA reviews the importance of

1 these products in the regulatory and public
2 health considerations. I'm related to a PMTA.
3 Impact is so important. It's what we live and
4 breathe. It's what I think FDA do, and I'm
5 impressed each time I meet with so many people at
6 FDA when they see the promise of ENDS that I
7 think there's a shared interest and potential for
8 such products and to truly make a positive impact
9 on public health.

10 I wanted time to just a couple of
11 brief comments on the compliance which was
12 initially the focus of this session. FDA's
13 extension of the compliance date to 2022 for
14 these products and for filing ENDS PMTAs really
15 was very welcome by the industry and it continues
16 to be extraordinarily important for many
17 companies.

18 It recognized the complexity of the
19 requirement for PMTA friends that the draft
20 nature of the guidelines as exceed the
21 expectations appear to be involving. And the
22 value of providing more time for PMTAs that would

1 be informed and by far the thinking of guidance
2 from FDA including final guidance, which we
3 haven't seen yet.

4 As additional time gives us more time
5 for emerging signs that can reach the data and
6 the applications, cleaner direction from CTP,
7 reach expectations and final guidance meetings
8 like this, and scientific advice meetings.

9 And I think today has gone a long way
10 to assist in that process and to better able to
11 manage some of the longer lead time items that
12 are clearly take time to do well in a context of
13 a PMTA program.

14 I should say that I -- and we,
15 generally, we are very bullish about what we have
16 to bring to the public health in this area. I'm
17 bullish about the potential for ENDS products as
18 valuable products for achieving PMTA. I come to
19 this with a note of optimism. I haven't felt all
20 of the that throughout the last couple of days,
21 but I'm very optimistic about what we have ahead
22 of us, what we can bring to this, and the impact

1 that we will on the population.

2 And I look forward to making a robust
3 submission. We are encouraged by the
4 unprecedentedly positive impact of ENDS on an
5 adult active smokers. You see population effects
6 in a way that you don't see on NRT and it's
7 exciting.

8 We're also cognizant of the importance
9 of responsible actions to mitigate unattended
10 consequences for non-smokers, and really
11 confident about putting that positive benefit in
12 public health.

13 So I'll close by saying just how
14 appreciative I am of FDA's efforts to inform
15 potential applicants and stake holders of its
16 expectations. I would encourage and underline
17 the comments that were made yesterday about
18 scientific advice meetings and the value of these
19 meetings with the agency, and the several
20 meetings that I've had in my different rules. I
21 found the FDA to be extremely helpful,
22 informative in these such meetings, and I

1 encourage all colleagues to take advantage of
2 that opportunity. Thank you.

3 MS. JOHNSON: Thank you, David. Drew.

4 MR. NEWMAN: Thank you very much.

5 It's very interesting to be paired here on this
6 panel with David because we represent brand new
7 state of the art technology and old world
8 tradition.

9 My name is Drew Newman and in 1895 my
10 great-grandfather J.C. Newman founded our family
11 business, and four generations and a 123 years
12 later we're the oldest family owned premium cigar
13 company in America.

14 My family rolls premium cigars in our
15 historic cigar factor in Tampa, Florida using
16 antique hand-operated semi-automated machines,
17 and we also roll cigars by hand in Nicaragua.

18 Actually, many of here in this room
19 have actually been to our factory and toured it a
20 couple of years ago and more recently. And if
21 you haven't come -- been there, please come down
22 and visit us in Tampa. My father, Uncle, and I

1 would love to show you around and show you how we
2 roll premium cigars here in the United States.

3 And if you're not familiar with the
4 premium cigar, let me tell you. They're all
5 natural hand-crafted products. We roll them
6 today the same way that my great-grandfather did
7 a hundred years ago. The process has literally
8 been the same for more than a century.

9 We sale our premium cigars to about
10 3,000 retailers throughout the United States.
11 These are small Mom-And-Pop family businesses
12 with just a handful of employees. If you've
13 never seen one, there's actually a nice cigar
14 store called Signature Cigars about a mile down
15 the road that way, down Rockville Pike. Please
16 pop in and you can really see our industry on the
17 market place.

18 Premium cigars are different. They're
19 just three percent of the cigar industry in
20 America and they make up one half of one percent
21 of the tobacco industry as a whole. We are a
22 tiny sliver of the tobacco world. And we're made

1 up of a bunch of old family businesses just like
2 ours and most are very small.

3 When someone asks me, "What's a
4 premium cigar? What is it?" I usually turn to
5 wine because the process of making wine is
6 remarkably similar with making a hand-crafted
7 premium cigar.

8 Just as the soil, sunlight, wind,
9 rain, all cause a Merlot grape grown in a
10 vineyard in France that tastes different than the
11 same grape grown in California, the same is true
12 with premium cigar tobacco.

13 And just as with wines certain
14 vintages or years are known to be better than
15 others, and the same is true with premium cigar
16 tobacco. And just as aging your beautiful red
17 wine can make it better over time, the exact same
18 thing is true with premium cigars.

19 And like old world French wine makers
20 who blend together a different grape varietals to
21 create unique tasting wines, as cigar makers, we
22 do the exact same thing with premium cigar

1 tobacco.

2 We harness the natural variation in
3 premium cigar tobaccos to make interesting blends
4 with limited production, low volume runs just as
5 wine makers do with grapes. None of that is
6 standardized. None of that is written down.
7 None of that is formulaic. It's not a science.
8 It's an art and the tradition has been passed
9 down from generation to generation.

10 It's important for FDA to appreciate
11 the patterns of use for premium cigars are
12 distinct from other products. Recent pass study
13 data have shown that the typical premium cigar
14 smoke in America consumes 1.7 premium cigars a
15 month. Ninety-seven percent American premium
16 cigar consumers smoke cigars exclusively and the
17 same 97 percent smoke fewer than one cigar per
18 day. And the past study also show is there is no
19 statistically significant use of premium cigars
20 by youth.

21 My point here is that premium cigars
22 are an old world hand-made craft enjoyed by

1 adults. This is why we are very worried about
2 FDA regulation. A year from now our HPHC reports
3 are due, yet no premium cigar company knows what
4 to do.

5 Premium cigars come in a wide range of
6 shapes and sizes. How are we supposed to test
7 them? There's no international standard for
8 testing along filler hand-made cigar with a
9 thousand the size they come in.

10 We are even more worried about SE
11 reports. There are tens of thousands of SKUs
12 sold today and no one knows how to file those
13 tens of thousands of SE reports for premium
14 cigars. The guidance is unworkable and we need
15 your help in understanding what to do.

16 For this reason, I'll wrap up by
17 saying that we are very grateful for the agency's
18 compliance policies which have given us breathing
19 room, and we thank Commissioner Gottlieb,
20 Director Zeller, Dr. Holman, and all of you here
21 for listening to us and wanting to work with us.

22 And the last thing I want to say is

1 that our one goal for our company is that we want
2 to be here 123 years and four generations from
3 now continuing this tradition and this art.

4 We welcome your questions and we look
5 forward to visiting, to working with you, and
6 please come and visit us in our historic cigar
7 factory in Tampa.

8 MS. JOHNSON: Thank you so much, Drew.
9 So as Dr. Holman said this panel discussion will
10 be a little bit different. We're not going to
11 have the cards, but we do invite folks who have
12 questions to sign here, start the line this way,
13 come to the mic. If David and Drew -- you all
14 have comments and questions as well please feel
15 free to interact.

16 So this is a listening session.
17 Anything that folks want to discuss about the
18 newly deemed tobacco products -- I was looking
19 for Spike. There you are. Here's your chance.

20 MS. BABAIAN: I never mind being
21 first. There's -- I spoke with a couple of
22 members from FDA to ask about the process and

1 about getting through PMTs.

2 Vapor products are new products. We
3 don't have standardized testing methods. We
4 don't have standardized products. We don't have
5 products to compare to. We don't have products
6 from ten years ago that we can compare against.

7 I wrote the first study with a
8 university upstate on vapor toxicity in the
9 United States. In 2009 to 2011 we worked on it.
10 It took two years and \$150,000 to publish a very
11 small study just to determine toxins in by-
12 products from vapor, and this was using a
13 machine. No subjects, no in vivo, in vitro.
14 Using a machine and a bag to test the air.
15 \$150,000 and two years to do it, and we basically
16 did two flavors.

17 Tobacco and no flavor because we
18 wanted to see whether flavors were potentially
19 harmful by-products from flavor additives, so we
20 did flavorless and flavored, and it cost that
21 much money.

22 The required testing for the PMTAs,

1 for any vapor company, small company, even NJOY
2 is going to be exorbitant. There's no way that a
3 vapor product can -- a vapor company, that
4 manufacturer can afford to do the requiring
5 testing to get through the PMT process, and so
6 the concern is that with of the varieties and all
7 of the different styles, and all the different
8 types, and all the different modifications that
9 you have for vapor products and no history, no
10 record -- we had to find puffing topography to
11 determine the length of time for a puff just to
12 be able to do the study with a machine.

13 And we had to readjust the machine to
14 four seconds instead of two seconds and there's
15 so much to do that it's almost impossible to
16 think anyone will get through it.

17 And I'm not saying that the people
18 aren't going to try, but I think that there's
19 another alternative. I think that there has to
20 be a way to set up a vapor approval process. I
21 know at this stage of the game it's a little
22 late, but I'm begging for someone to please

1 rethink this.

2 I think there needs to be a way to
3 study what's in the liquid to determine
4 ingredients, to determine HPHC, determine voltage
5 levels, and level of heat that's required in
6 order to create these by-products, and say you
7 can't have a product that goes past that heat
8 level.

9 There are simple ways to make this
10 product available and make the testing affordable
11 and keep it accessible to people who smoke
12 cigarettes that are killing them, so I'm just
13 asking to please reconsider a better way to
14 regulate this product and regulate ingredients
15 and safety and battery safety and UL listing for
16 battery products without demolishing an industry.
17 And that's pretty much what I had to say. Thank
18 you.

19 MS. JOHNSON: Thank you, Spike. I'll
20 give you guys first crack. Have you had anything
21 to add or --

22 MR. GRAHAM: I guess I would just add

1 as I was coming closed in my earlier comments, I
2 do believe that through personal experience that
3 meetings with FDA are really very informative and
4 shining a path forward for such programs and
5 studies.

6 And you know we heard yesterday how
7 it's important to be thoroughly prepared in these
8 kinds of meetings and not to ask FDA to provide
9 the guidance that's already available and for
10 written, but to do ones homework and really look
11 between the lines of what's been guided already
12 in public.

13 And therein lies your uncertainty and
14 to go to the agency with proposals for their
15 review and consideration, and I personally have
16 benefited from quite a lot of learning and
17 experience from that, and I think people are
18 really genuinely there to try to help.

19 MR. NEWMAN: Thank you. I have
20 nothing directly to add to the ENDS topic, other
21 than we feel like we are in the same boat and we
22 would like to work with the agency and figure out

1 our historic industry can work within the
2 regulations.

3 MS. JOHNSON: Thank you. Anyone else?
4 Come on this is, like, exciting stuff, right? We
5 all have our armor on at CTPU -- we waiting to
6 hear from you all about this newly deemed
7 products. There's so much in the media. You all
8 have so much information and opinions. Come and
9 share with us.

10 So when you get up to the mic, just
11 remind us of your name and the company that
12 you're with, please.

13 MS. HAYDEN: Debbie Hayden, and I had
14 a question from really, from maybe earlier in the
15 day the other presentations that had to do with
16 the cigars since those are also newly deemed, and
17 the discussion about stability testing, and it
18 kind of pointed right at smokeless, which made me
19 wonder is there an expectation of stability
20 testing for the cigars because it made me think
21 maybe there isn't a lot of discussion about
22 what's should that stability testing look like,

1 so if anybody from the FDA has a thought on that,
2 it'd be helpful.

3 MR. NEWMAN: While they confer, maybe
4 I can just say that we share your concerns. I
5 was taking lots of notes during the stability
6 testing section just because we know that this
7 cigar has eight year old tobacco in it, and we
8 know that it was rolled last year, and we know
9 that if it ages five years it will taste
10 different than it does now, just like wines or
11 scotch or distilled spirits.

12 And also know that if I let the cigar
13 outside it's going to dry out and the moisture
14 content will change and it really worries us
15 about this type of testing.

16 MS. JOHNSON: So we're going to take
17 that back and take that under advisement.
18 Appreciate you bringing that to our attention.
19 Thank you, Debbie.

20 So what did you all have to eat for
21 lunch? You're so quiet. This morning you were,
22 like, whoa. Now, you're so quiet. Okay. So I

1 know you're still alive because you laughed at my
2 dumb joke. Great. Don't forget to tell us your
3 name and your affiliation, please.

4 MR. BECKER: My name is Don Becker and
5 I'm with Turning Point Brands. And the question
6 that I had is I realize that these reviews are to
7 be considered on a case-by-case basis for
8 different products, but there are so many
9 different products out there. And as Mr. Newman
10 explained it's impossible to create such a burden
11 upon industry to have hundreds of thousands of
12 combinations per company.

13 In some cases you can have a million
14 plus combinations for a single company, and I'm
15 just thinking in other areas of Government,
16 including payment of income tax. You know, the
17 IRS doesn't say, here are the things you might
18 want to consider.

19 At the very least they do provide some
20 better guidance in terms of a tax form. Fill in
21 these sections. And I'm thinking for SEs and
22 exemption request and things like that, it really

1 should be able to be reduced to a form. And some
2 things may not apply, there may be a supplemental
3 form. It just seems to be a natural progression
4 to have some things improved so that expedited
5 review of SEs and exemption requests, and even
6 parts of the PMTA to be supplemented with custom
7 studies and things like that were appropriate for
8 the protection of the public health.

9 But sometimes it feels like some
10 circular references to consult the guidance and
11 these are the things to consider and don't forget
12 to consider and FDA would recommend, but that's
13 not helpful in us in determining how much it's
14 going to cost, how much time is involved, how
15 many people are getting involved.

16 We start to consider which SKUs we're
17 going to carry in a few years and I'm just
18 looking for maybe some better guidance in that
19 regard. Is something else coming to help us to
20 be more clear? This is a great start by the way,
21 but just looking for something.

22 MR. NEWMAN: I completely agree. The

1 idea of an income tax like form with instructions
2 can be really helpful. You know as Thomas was
3 saying earlier when he was up here the technology
4 involved in making one of these is a ruler and a
5 table, and a knife.

6 And because of that in our industry
7 there are so low barriers to entry there are
8 dozens and dozens of tiny little companies and if
9 we are in the -- at the process or completing of
10 SE and HPHC testing involves consultants and
11 complex forms and everything. It's going to be
12 the five of us in the handmade cigars industry
13 from the back of the room left and all of these
14 small businesses that have been around for a long
15 time are not going to be able to compete and the
16 market is going to get squeezed.

17 MS. JOHNSON: Thank you. David,
18 anything to add?

19 MR. GRAHAM: No.

20 MS. JOHNSON: No. All right. Further?

21 MR. ANTON: Good afternoon. My name
22 is Mark Anton. I'm the Executive Director of the

1 Smoke Free Alternatives Trade Association and we
2 represent a lot of small businesses in this vapor
3 category.

4 And one of the things I wanted to ask
5 is with all of these standards, proposals,
6 directions, guidance, how is a small business
7 person supposed to actually do these things when
8 we see over three million submissions for SKUs
9 for different flavors, for different PG/VG
10 ratios? And if the FDA, when they deemed this,
11 they said this would cost about \$300,000, well
12 that's over \$900 billion dollars and a market
13 segment about five billion.

14 So how is a small industry supposed to
15 stay in business? You've got vape stores. I
16 mean, Spike, she's had her store for years.
17 Those folks are the front lines. They're the
18 ones who are helping the smoker understand the
19 complexities of the products and the deliverables
20 to help them to transition.

21 How is a business like that supposed
22 to stay in business when they potentially won't

1 have products to sell? Thank you very much.

2 MS. JOHNSON: Comments from the
3 panelist? Those are very good points.

4 MR. GRAHAM: Again, I think the
5 question is really leveled to FDA, and I think
6 FDA positions itself to be able to respond to
7 uncertainty of this sort, and I would encourage
8 colleagues in the industry to make best outreach
9 to the agency.

10 I think if that's not fruitful then
11 it's even more frustrating, but personally, I
12 haven't seen evidence of that, and I think all I
13 could comment on is to use every available
14 resources there including that that's not written
15 such as what FDA is willing to offer.

16 MS. JOHNSON: Thank you.

17 MR. NEWMAN: The only thing that I'll
18 add is think about handmade cigars and think
19 about the cost of compliance with SE, HPHC
20 testing and so forth.

21 It makes me wonder what the cost
22 benefit analysis really is. Particular with our

1 products are used and frequently bought by adults
2 and whether the high cost of compliance so far is
3 a good efficient use of Government resources
4 and/or there's a better way to achieve the same
5 result, the same benefits, but in a way that
6 allows the industry to continue.

7 MS. JOHNSON: Thank you. Any other
8 comments? Any further comments?

9 (Off microphone comments.)

10 PARTICIPANT: Regards to cigars, there
11 are standardized methods out for cigarettes of
12 Canada (Phonetic) and iso-smoking regimes, for
13 example, but there are no clear guidelines for
14 cigars, and what to do. There are also no
15 reference products. I was hoping you could
16 provide some comments on that as the FDA. And,
17 whether to follow the CORESTA recommended methods
18 which are continually changing and are in review
19 now or going to isolate.

20 MR. NEWMAN: That's a great point. It
21 worries us, like, on the cigarette side there's a
22 well-developed testing regime. There are standard

1 sizes and those sizes have billions and billions
2 of units. There are a thousand different sizes of
3 cigars.

4 This is a Toro at about six inches
5 long. This is a Corona it's shorter, it's
6 thinner. This is a Robusto. These are three of
7 about a thousand sizes in the same brand family,
8 and we're looking to CORESTA in the international
9 community to help us think about the testing
10 regimes.

11 But how you create a scientific
12 standard for wide variety -- products that come in
13 a wide-variety of sizes and it's a challenge. And
14 there's also research showing too that consumers
15 consume different cigars in different quantities.
16 Some will smoke the entire thing, the other will
17 put it down after a quarter of an inch, or half an
18 inch.

19 So trying to create something that's
20 realistic and achievable and is cost effective
21 when we're dealing with such low volume quantities
22 and products is a real challenge and it worries

1 us.

2 (Off microphone comments.)

3 PARTICIPANT: Thank you. And also, a
4 follow up question. Could you comment of machine
5 made cigars which are still basketed with products
6 like cigarettes? Do you have comments on that?
7 And, how to test those as well?

8 MR. NEWMAN: Sure. Well, when I think
9 of testing in machine-made products there was a
10 study that came out and I believe the nicotine and
11 tobacco research journal about a year ago, and it
12 was done by some FDA colleagues over there who
13 bought a set of cigars in 2015.

14 Bought the same cigars on market in
15 2016 and did a host of test on them and they found
16 wide ranges of differences in nicotine and other
17 HPHC from one year to the next just given the
18 natural variations.

19 I think most of those products were
20 machine-made. There was a Monte Cristo cigar,
21 handmade cigar in that cohort too, but it just
22 suggest to me that our products really are subject

1 the natural variations of nature, and so trying to
2 apply a strict scientific regime to a product that
3 is inherently natural and handcrafted is a real
4 challenge.

5 MS. JOHNSON: Thank you. Any other
6 comments or thoughts, or observations? Okay.

7 Well, let's thank our panelist David
8 and Drew. Appreciate you coming. Thank you so
9 much. And now, I will turn it over to
10 Dr. Holman to kind of bring these two days
11 together and wrap everything up.

12 MR. HOLMAN: So before Joe and I
13 present our closing remarks, what I'd like to do
14 since we have some extra time -- where did the
15 microphone go? If we can get the microphone back.

16 I mean, one of the things you'll hear
17 in my closing remarks, and hopefully, you picked
18 up yesterday in the opening remarks is, you know,
19 we put on this two-day meeting as a way to
20 dialogue with stake holders we hope in a
21 productive effective way.

22 We debated the format, how to do this,

1 how to best accomplish that goal of having that
2 dialogue, and I think it would be useful to hear
3 from participants, attendees in the room. If
4 you're comfortable stepping to the microphone,
5 just sort of sharing, you know, how well this
6 meeting worked or didn't work and just give us
7 some honest feedback.

8 I've asked Joe if he wouldn't mind sort
9 of kicking off that discussion with his own
10 observations, which he's agreed to, but after Joe
11 is finished speaking on that if others feel like
12 they want to come up to the microphone, we're
13 happy to take that feedback.

14 So do you want to do it from there?

15 MR. MURILLO: Yes. This is fine. Am
16 I on? Yes?

17 MR. HOLMAN: Yes, it's green.

18 MR. MURILLO: Okay. So thank you,
19 Matt. I'm Joe Murillo, Senior Vice President of
20 Regulatory Affairs for Altria. As most of you
21 know Altria is a holding company. We own a series
22 of tobacco companies including Philip Morris USA,

1 U.S. Smokeless, Matt Sherman, John Middleton, and
2 Nu Mark.

3 I will tell you that first I will add
4 my thanks to tell Matt and to the FDA for putting
5 this together. I will also tell you that in terms
6 of the dialogue this is one of the first times
7 that I really felt acknowledgment from the agency
8 as our regulator for some of the issues that we've
9 been facing, almost in some cases empathy, and I
10 have to say goes a long way. At least we're
11 hearing each-other. You're hearing that we have
12 some questions, we have some frustrations, we have
13 some issues, and that helps.

14 You acknowledge that we need rules.
15 You've acknowledged that there's been some
16 evolution. You have acknowledge that there are
17 some difficulties remaining. You've acknowledged
18 that everybody would like there to be better
19 dialogue.

20 The second thing that I would say that
21 we should remember that we are unique in this area
22 and in this country for having this inclusive

1 approach to regulatory proceedings and dialogue.
2 I've been with Altria for more years than I'm
3 going to mention right now, but before this
4 assignment I've had other assignments where I've
5 dealt with regulators abroad and there is not this
6 sort of dialogue that I can think of just about
7 anywhere.

8 In terms of the feedback and the most
9 effective exchanges, I think that exchanges that
10 assumed basic knowledge were more productive. So
11 in other words, if we ask a question that is
12 carefully worded within the terms of the statute
13 and the guidance, and you answer the question with
14 carefully worded language that recites back to me
15 what I already know that's in the guidance that is
16 not a useful exchange to either one of us, right.

17 So I think the flip side is you have to
18 come prepared. The regulator should be entitled
19 to assume or tell us that they will assume, that
20 they will assume basic knowledge of what's already
21 in their statute and the guidance, and if people
22 have scoured the website to find every last bit of

1 feedback that is available, and then you can ask
2 a more insightful or relevant question.

3 In that regard, I thought that one of
4 the things that worked particularly well yesterday
5 and today is the level of detail in examples that
6 were provided by the agency. I think the detail
7 in examples we got yesterday with respect to the
8 SC process was terrific. It, for us, confirmed
9 some things we've been seeing in recent letters.
10 In some other cases it caused us to sort of ask
11 around, hey, did you see that, is that what they
12 meant? And I think that was very helpful.

13 Dialogues that are two-way that allow
14 for Q&A are the best. Because of unfortunate
15 circumstances we couldn't have that in this very
16 last session that we just went through, but with
17 that as an exception because of the circumstances,
18 I think situations like this where I can be
19 sitting in a room with some of the people who only
20 know me because I sign letters or I only know them
21 because they sign letters back to me is very
22 helpful.

1 I think with that level of detail an
2 improvement would be maybe starting to tiptoe
3 toward areas, new areas, where we can apply these
4 learnings and observations to future issues,
5 right. So can we be comfortable, can we become
6 comfortable starting to talk about how will we
7 think about HPHC for cigars. What will we do with
8 analytical variability? Are there some parameters
9 that we might think about with respect to design
10 issues?

11 I mean, I was listening to Mr. Newman.
12 I have no idea how we're going to get certificates
13 of acceptance, etc., etc. for design parameters
14 for cigars in the premium area.

15 Same with vapor and I think we heard
16 some useful beginnings of conversations with
17 respect to HPHC and also some, I think
18 evolutionary dialogue with respect to the very
19 serious youth issue. Dr. Gottlieb has talked
20 about the youth epidemic. I don't see how we're
21 going to be able to achieve PMTAs for some of
22 these products without more directly addressing

1 the potential for youth appeal.

2 Other feedback that I have written down
3 is that you ought to make sure you're posting some
4 of this information in real time. So we talked
5 about things that, you know, we got in FOIA or
6 someone else has gotten. We talked about the
7 attachment that is going with SC letters, etc.,
8 etc. If there are memos that people can get
9 through FOIA in any event or things that you are
10 sharing at a conference, why not post it? Maybe
11 even post before the conference so we can study it
12 and come with deeper questions.

13 We talked a little bit about a
14 different way of communication which is potential
15 dialogues during the review process. And I
16 understand the difficulty with having deep
17 conversation in the review process, however,
18 clarifying questions are not always the most
19 effective. I mean, we've used them but it kind of
20 -- I suspect leaves both sides hanging sometimes
21 saying, gee, if I could only ask the applicant of
22 a follow-up and that may save me 40 hours of work

1 or something, and maybe there's a little bit more
2 that could be done there.

3 And then my final suggestion in terms
4 of feedback would be workshops like this and
5 workshops of this nature on specific topics.

6 So for example, we started to touch on
7 population effect issues and post market
8 surveillance and youth appeal issues. These are
9 very thorny topics and we don't have a lot of
10 history yet in the PMTA program, in fact, we have
11 precious little to be able to draw conclusions or
12 draw examples from that. Maybe a format could be
13 developed where both sides could be comfortable
14 having some sort of workshop type dialogue on more
15 specific issues that are relevant to applicants
16 and reviewers. So those are some thoughts.

17 MR. HOLMAN: Great. Thank you. If
18 others want to step up the microphone and share
19 any of their thoughts, we'd be glad to listen.

20 Again, please state your name and your
21 affiliation for the transcriber.

22 MS. BABAIAN: Spike Babaian. New York

1 State Vapor Association. I liked your thought on
2 topic specific meetings. It might be helpful to
3 potentially letting the vapor industry survive if
4 there were discussion of testing methods that we
5 could use since there aren't standardized testing
6 methods yet, and maybe putting together something
7 on how we can assess different things that affect
8 us.

9 Environmental assessment for vapor
10 products that don't have side streams smoke and
11 don't have -- you know, there are a whole
12 different realm of tests for us that are going to
13 be required. And I think there is a potential for
14 more companies to maybe make it through if they're
15 working together to use, you know, bridging
16 research if we can get together to do that. And
17 with the FDA's help that might be a possibility,
18 so that would be appreciated.

19 MR. HOLMAN: So just to wrap things up.
20 First I want to thank all of my colleagues in the
21 back of the room and those that are aware in the
22 hallway for doing a lot of prep work to make this

1 meeting happen, doing a lot of behind scene work
2 yesterday and today to make sure that the meeting
3 goes on as planned, so big thanks to them.

4 I would also like to thank all of my
5 colleagues who gave presentations of the last two
6 days. I particularly thank those that sat on the
7 panels and took some, I think some good, honest
8 feedback. And so, again, thank you guys for your
9 participation in making this meeting a success.

10 I would also like to thank the panelist
11 for be willing to sit up here and be candid and
12 share their perspectives, share their concerns
13 with us, and so, that we can have a productive
14 conversation and dialogue about some of these
15 issues, so.

16 And then lastly, thank all of the
17 participants both of those in the room as well as
18 those viewing remotely for all the questions.
19 Obviously, those questions generate a lot of good
20 discussion and brought out a number of issues that
21 otherwise would not have been brought out, so
22 again thanks for everyone for active engagement in

1 this meeting in order to make it as successful as
2 it could be.

3 In terms of goals we had for this
4 meeting coming into it, you know, the goals I
5 jotted down as I was listening for the last couple
6 of days thinking, you know, what do we set out to
7 do and how well do we do it. I think we actually,
8 in my mind at least, personally I view this as a
9 very successful dialogue over the last two days.

10 As you guys heard over a little bit,
11 over a year ago Commissioner Gottlieb asked us to
12 really assess, evaluate our application review
13 programs. We certainly had been doing that in
14 this meeting as it was meant as a way to bring to
15 light. I think to make more public some of the
16 things we've been doing to really assess our
17 application review programs to determine how we
18 could maybe operate in more efficiently and
19 effectively in evaluating applications.

20 So some of the specific goals are that
21 we wanted to share information that we hoped would
22 be useful to stake holders ranging from those

1 companies who have not yet submitted a marketing
2 application, which we heard from just a moment ago
3 to those who maybe have extensive experience and
4 have submitted numerous applications to us, and
5 have interact with us in a variety ways. And so
6 we hope that there's information really for all
7 the manufacturers from the small to the big that
8 you found useful over the last two days.

9 Another goal that we sat out to achieve
10 that I think we did a good job of is really just
11 laying out for you guys sort of the evolution of
12 our programs over time. Obviously, the SC and EX
13 have evolved much more than PMTA at this point
14 because we've got a lot more experience both at
15 our end and at the applicant's end, and those two
16 programs.

17 And we've also heard a lot of feedback
18 over the years about those programs because of the
19 experience. And hopefully, what you've seen today
20 or heard today and yesterday that is that we do
21 listen, we do hear these things and we do try to
22 have the programs evolve in a very positive way

1 based on those experiences and our own direct
2 observations as well as what we hear from other
3 stake holders about the programs.

4 And then lastly, we were really hoping
5 for a conversation. We were looking at this as an
6 opportunity to solicit feedback and ideas for
7 places where we could improve for ideas of how we
8 could improve in some of our programs and further
9 evolve them. I think what made it successful
10 discussion or conversation from my perspective is,
11 you know, I thought it was a very balance, fair,
12 perspective shared by all participants. A very
13 respectful tone to the conversation, which I think
14 it is imperative because it doesn't always exist
15 in all forums.

16 And also, the candidness, I think we
17 can only learn as much as what's shared with us
18 and I think folks willing to be candid and share
19 their perspectives, share some of their concerns
20 and the reality that they're dealing with is very
21 helpful to us. So I do appreciate that.

22 I heard a lot of things over the last

1 couple of days so I want to note some of the
2 feedback I heard and particularly some of the
3 things that really got my attention, but I figured
4 it would be funner for you guys to guess what got
5 my attention, so I'm going to leave it at that.

6 Any guesses Joe?

7 No, all in seriousness, I mean, I was
8 jotting notes the whole day, yesterday and today
9 on a lot of good feedback and a lot of good ideas.
10 I'm just going to capture a few of them and share
11 some of my thoughts or provide, maybe in some
12 cases more information.

13 On one of things that was talked about
14 a lot of the last two days are industry meetings.
15 I think one of the realizations that I've had
16 recently is that maybe our message about industry
17 meetings and our advice to applicant's to be very
18 thoughtful and careful about when they submit, how
19 many they submit. Maybe that message went a little
20 too far. And maybe folks aren't utilizing those
21 pre-submission meetings to the extent that they
22 can, and so I just want to encourage folks.

1 You heard David Graham, for example, in
2 the last session talk about how useful they can
3 be. I think they are a great tool that maybe is
4 being underutilized and maybe that's partly our
5 fault for the messaging around those industry
6 meetings. But I would certainly encourage you to
7 submit meetings before you submit your
8 applications.

9 But also I would say be thoughtful
10 about the topics and how you frame those meetings
11 because they are only successful as -- they are
12 only going to be as helpful to you as based on how
13 well you ask the questions that you need to ask of
14 us. And I think we've seen, internally, as we do
15 these -- that some of those I think we view as
16 very productive for the applicant. I think other
17 times we review them probably is not all that
18 helpful to the applicant, and that's really based
19 a lot upon the questions that get asked of us and
20 information that gets shared with us.

21 As an example, we sometimes get asked,
22 like, here's my whole plan for submitting a PMTA,

1 will this get me a marketing order? Can't tell
2 you that, right. But on the other hand we get
3 other very specific questions, like, you know,
4 here's the clinical studies that we think might
5 possibly support our market, you know, marketing
6 order under these applications, do you have any
7 concerns with the study design, the study size,
8 anything like that? Very specific questions where
9 we can say, no, we don't have any concerns that
10 looks like a study design that might work. Or we
11 might say, yes, we do have concerns we think it's
12 under powered or something along those lines.

13 So again, as you think about submitting
14 meeting requests just be very careful about, you
15 know, what you're asking and make sure you really
16 get out of that meeting what you're hoping to get
17 out of it.

18 Another area that we certainly heard
19 over and over again is just more regular and
20 improved communication with applicants. You know,
21 today is part of that, but we need to do more,
22 we're trying to do more, we're trying to utilize

1 the website in better ways. I think we heard some
2 good ideas, some good comments about the content.

3 For example, yesterday and how easy or
4 difficult it might be to find some of the
5 information on the website, but there are a lot of
6 tools that we can use to communicate. This
7 meeting today and yesterday is one of those tools,
8 but there were other variety of other tools that,
9 you know, were exploring how to best utilize them
10 to improve communication beyond where we are
11 today.

12 And then lastly, another issue that
13 came up yesterday was just talking about and
14 today, talking about electronic submissions. You
15 know, we view that as a tool to help applicants to
16 make submission to us easier than it could be, but
17 we're also hearing that sometimes that there are
18 challenges there that we need to try to work on
19 tackling. But we did hear that there is some
20 interests or some companies that are following the
21 CDT model for their applications and heard that,
22 that seems to work well.

1 So again, we're going to take that back
2 and figure out what we can do with that and how we
3 can facilitate electronic submission of the
4 applications.

5 So just to wrap things up, again I
6 think this is, in my view, was a pretty successful
7 meeting. I hope all of you feel the same as well.

8 And again, as I said earlier, I think
9 that all goes to active participation by all
10 attendees and not just, you know, FDA up here
11 speaking. I think we saw that it was very helpful
12 to hear all of those perspectives.

13 Also would remind you that the docket
14 is open and it will stay open after this meeting,
15 and so if there is additional thoughts or ideas
16 that you didn't get to share or that came to you
17 during the meeting, but you didn't have the
18 opportunity to share them with us, certainly,
19 submit those to the docket. We will be evaluating
20 all those docket submissions after the meeting.

21 Our slides will be made available that
22 we presented over the last few days. They will be

1 made available on the website, hopefully, shortly
2 after the meeting.

3 And we hope to walk away from this,
4 again, with some ideas about how to better create
5 a dialogue going forward. You know, we hope this
6 is just not a one-time dialogue. That there are
7 ways we can maybe do things like Joe suggested
8 where we pick specific topics and have these types
9 of conversations around those topics.

10 So thank you all for your time. Thanks
11 for sticking around over the two days and engaging
12 really in the discussions here during this
13 meeting, so appreciate it.

14 MR. MURILLO: So thank you, Matt and
15 thank you for the opportunity to giving some
16 closing remarks from a regularity perspective.

17 Let me just say first that I would feel
18 reminisce if I didn't acknowledge the sad news
19 that Mitch shared with us yesterday to start the
20 meeting, and that is about the untimely passing of
21 David Keith.

22 David was a dedicated and able public

1 servant and those who have worked with him found
2 him to be approachable and collaborative. So on
3 behalf of all of us at Altria we send out
4 condolences to David's family and his many
5 colleagues at CTP and across FDA.

6 Now, turning to this event, I want to
7 add my thanks to the agency for hosting the
8 workshop. I'm encouraged by the open and
9 transparent conversations among the presenters and
10 panelist.

11 This is really important communication,
12 and in fact, we think a cornerstone of a
13 successful framework is effective, open and
14 ongoing communication.

15 And in the announcement for the meeting
16 Dr. Gottlieb stated that establishing a rigorous
17 predictable science based framework for the pre-
18 marker review of tobacco products is a key element
19 of our program.

20 Moreover, today and yesterday we heard
21 a lot about CTPs desire for consistency,
22 transparency, and predictability and that is, of

1 course, music to our ears.

2 I think this public workshop represents
3 a great step in advancing these initiatives. Not
4 only did it provide a forum for stake holders to
5 engage in collaborative and transparent fashion,
6 but also allowed the agency to hear direct
7 feedback on how to improve and potentially evolve
8 the framework.

9 This brings us back to the purpose of
10 the workshop to share of experiences, learn from
11 others, and hopefully, to contribute to a better
12 regulatory process and to foster innovation. We
13 all need to be on the same page regarding the
14 rules of the road. This much we seem to be
15 agreement on, and I'm going to take my own advice
16 and not tell you what you've heard me and my
17 colleagues say many times, which is that it's hard
18 to do that when the rules are not written down or
19 the subject of notice in comment rule making, and
20 I will move on without telling you the content
21 that we believe is necessary because you've heard
22 it before.

1 So in closing, I would tell you that we
2 encourage CTP to have more sessions like these and
3 other less formal exchanges where we can come
4 together and compare learnings, and exchange
5 actionable ideas in an appropriate way.

6 I think we can work together,
7 communicate effectively, and work to implement the
8 pathways that we've been given, particularly, to
9 allow innovated products that can reduce the harm
10 caused by tobacco to come to market and improve
11 the public health. Thank you very much. See you
12 soon.

13 MR. HOLMAN: Thank you everyone. Safe
14 travels.

15 (Whereupon, the above-entitled manner
16 went off the record at 2:43 p.m.)

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In the matter of: Tobacco Product Application Review

Before: US FDA

Date: 10-23-18

Place: Rockville, Maryland

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Court Reporter

NEAL R. GROSS

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