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

(8:31 a.m.)

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

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

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

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

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

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

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

presentations as we move throughout the day.

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

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

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

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

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

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

ventilation, and characterizing flavor.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

constituents or HPHCs.

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

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

It has facilitated our review of SE

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

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

electronically.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

It would facilitate our review to

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

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

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

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

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

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

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

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

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

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

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

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

fermented tobacco.

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

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

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

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

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

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

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

considerations of the effects of the change on public health.

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

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

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

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

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

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

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

complete and unaltered COAs from the manufacturing supplier.

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

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

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

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

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

same units of measure for new and predicate.

Another form of common deficiencies we find has to do with interchangeable materials. If you manufacture a new and predicate product that may be constructed using different interchangeable materials, then each unique combination of those materials is considered to be a unique tobacco product, and therefore would require a unique submission.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A third approach is to provide

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Until such rules are in place, we are

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

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

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

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

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

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

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

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

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

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

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

MS. JOHNSON: Thank you so much. Tom?

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

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

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

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

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

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

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

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

We submitted these peer reviewed

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

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

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

very, very low tech setup.

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

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

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

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

I practiced FDA law for over 30 years, primarily in the drug and medical device field. My practice has included participation in drafting and implementation of the Tobacco Control Act on behalf of a variety of small tobacco product manufacturers and associations. While representing those clients, I participated in the drafting of many dozen substantial equivalence reports for cigarettes and smokeless products and preparing responses to the various rounds of FDA follow-up correspondence.

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

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

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

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

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

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

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

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

Conduct basic research and allow a

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

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

MS. JOHNSON: Thirty seconds.

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

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

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

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

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

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

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

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

We wanted to have this dialogue

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

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

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

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

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

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

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

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

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

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

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

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

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

applications.

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

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

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

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

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

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

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

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

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

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

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

MR. SCHEINESON: Right.

MS. ROGERS: -- but it is very helpful

for our review. And we do request that information.

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

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

report?

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

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

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

MR. SCHEINESON: Great.

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

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

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

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

changes involved of this type of magnitude? We're certainly in the dark about this.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. JOHNSON: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. JOHNSON: Thank you.

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

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

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

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

MR. LINDEGAARD: Just one -- I mean I

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

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

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

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

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

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

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

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

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

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

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

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

predicate.

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

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

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

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

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

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

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

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

MS. JOHNSON: We have a couple more.

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

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

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

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

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

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

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

MS. JOHNSON: Thank you.

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

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

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

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

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

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

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

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

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

results of those.

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

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

the stability testing question.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

getting ahead of ourselves.

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

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

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

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

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

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

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

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

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

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

justification for the deviation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

temperature.

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

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

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

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

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

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

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

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

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

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

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

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

legally on the market.

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

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

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

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

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

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

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

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

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

in order to support meaningful interpretation of research findings.

FDA acknowledges that it may not be feasible to directly measure the rate of uptake of a new tobacco product in a population, especially if it's never been on the market. Even if a product is on the market, there may not be sufficient number of users to directly study initiation in an observational setting.

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

factors that influence such change.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicants have asked if youth

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

product?

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

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

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

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

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

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

exposures.

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

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

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

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

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

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

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

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

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

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

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

development, may be appropriate to support a PMTA.

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

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

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

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

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

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

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

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

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

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

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

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

Does the scientific evidence provided

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

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

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

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

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

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

So therefore, a well-organized table of contents and functional hyperlinks really help the reviewer go through the submission. Applicants have sent new study data and large amendments to FDA for review towards the end of the FDA scientific review phase. So reviewing additional information has caused delays in FDA issuing of marketing or no marketing order.

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

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

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

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

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

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

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

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

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

MS. RUDOLPH: And I just have a quick

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

So now, I'll step through in a bit

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

product category.

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

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

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

TPSAC provides recommendations to FDA on the MRTPAs.

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

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

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

issuing a determination.

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

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

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

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

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

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

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

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

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

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

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

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

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

The application sections that have been proposed include descriptive information,

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

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

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

in terms of what we mean by all documents.

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

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

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

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

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

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

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

those listed in the -- in the first column.

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

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

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

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

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

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

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

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

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

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

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

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

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

sets, or federal restricted use data sets.

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

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

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

Producing focused FDA background materials for the Committee, streamlining the

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

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

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

head into lunch.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. RUDOLPH: Thank you, Matt. Elaine?

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

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

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

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

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

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

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

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

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

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

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

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

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

helpful.

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

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

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

And then, you know, getting a little

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

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

MS. RUDOLPH: Thank you, Elaine. Mohamadi?

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

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

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

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

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

Also, around the standard of the

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

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

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

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

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

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

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

You know, we think that such evidence

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

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

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

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

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

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

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

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

MR. APELBERG: Hi. Ben Apelberg, Director of the Division of Population Health Science.

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

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

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

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

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

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

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

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

I, you know, I flagged a few things.

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

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

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

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

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

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

MS. RUDOLPH: Thank you.

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

QUESTIONS AND ANSWERS

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

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

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

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

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

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

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

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

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

So if it's a product chemistry

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

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

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

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

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

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

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

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

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

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

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

MS. RUDOLPH: Thank you.

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

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

MS. RUDOLPH: Yes.

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

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

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

our tools for measuring post-market surveillance are slow.

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

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

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

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

MS. RUDOLPH: It's for whoever --

MR. APELBERG: -- for the industry?

MS. RUDOLPH: -- wants to take it. Jump in, whoever --

MR. APELBERG: Maybe the industry should --

MS. RUDOLPH: -- wants to go.

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

MS. RUDOLPH: Okay, thank you, Mohamadi.

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

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

the product to penetrate into the market.

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

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

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

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

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

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

The challenge there is, instead of

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

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

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

MS. RUDOLPH: And Debbie?

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

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

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

MS. RUDOLPH: Okay. Matt?

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

MS. RUDOLPH: No, please.

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

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

extraordinarily attractive.

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

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

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

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

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

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

MR. APELBERG: Sorry.

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

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

attract.

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

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

MS. CALLAHAN-LYON: Is that vague enough?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Off microphone comments.)

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

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

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

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

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

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

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

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

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

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

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

PARTICIPANT: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

committee.

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

(Off microphone comments.)

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

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

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

MS. CALLAHAN-LYON: Okay. So an

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

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

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

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

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

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

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

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

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

session back to our colleagues at Office Compliance and Enforcement.

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

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

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

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

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

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

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

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

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

And how FDA reviews the importance of

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

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

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

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

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

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

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

that we will on the population.

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

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

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

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

MS. JOHNSON: Thank you, David. Drew.

MR. NEWMAN: Thank you very much. It's very interesting to be paired here on this panel with David because we represent brand new state of the art technology and old world tradition.

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

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

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

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

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

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

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

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

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

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

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

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

tobacco.

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

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

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

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

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

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

For this reason, I'll wrap up by saying that we are very grateful for the agency's compliance policies which have given us breathing room, and we thank Commissioner Gottlieb, Director Zeller, Dr. Holman, and all of you here for listening to us and wanting to work with us.

And the last thing I want to say is

that our one goal for our company is that we want to be here 123 years and four generations from now continuing this tradition and this art.

We welcome your questions and we look forward to visiting, to working with you, and please come and visit us in our historic cigar factory in Tampa.

MS. JOHNSON: Thank you so much, Drew. So as Dr. Holman said this panel discussion will be a little bit different. We're not going to have the cards, but we do invite folks who have questions to sign here, start the line this way, come to the mic. If David and Drew -- you all have comments and questions as well please feel free to interact.

So this is a listening session. Anything that folks want to discuss about the newly deemed tobacco products -- I was looking for Spike. There you are. Here's your chance.

MS. BABAIAN: I never mind being first. There's -- I spoke with a couple of members from FDA to ask about the process and

about getting through PMTs.

Vapor products are new products. We don't have standardized testing methods. We don't have standardized products. We don't have products to compare to. We don't have products from ten years ago that we can compare against.

I wrote the first study with a university upstate on vapor toxicity in the United States. In 2009 to 2011 we worked on it. It took two years and $150,000 to publish a very small study just to determine toxins in by-products from vapor, and this was using a machine. No subjects, no in vivo, in vitro. Using a machine and a bag to test the air. $150,000 and two years to do it, and we basically did two flavors.

Tobacco and no flavor because we wanted to see whether flavors were potentially harmful by-products from flavor additives, so we did flavorless and flavored, and it cost that much money.

The required testing for the PMTAs,

for any vapor company, small company, even NJOY is going to be exorbitant. There's no way that a vapor product can -- a vapor company, that manufacturer can afford to do the requiring testing to get through the PMT process, and so the concern is that with of the varieties and all of the different styles, and all the different types, and all the different modifications that you have for vapor products and no history, no record -- we had to find puffing topography to determine the length of time for a puff just to be able to do the study with a machine.

And we had to readjust the machine to four seconds instead of two seconds and there's so much to do that it's almost impossible to think anyone will get through it.

And I'm not saying that the people aren't going to try, but I think that there's another alternative. I think that there has to be a way to set up a vapor approval process. I know at this stage of the game it's a little late, but I'm begging for someone to please

rethink this.

I think there needs to be a way to study what's in the liquid to determine ingredients, to determine HPHC, determine voltage levels, and level of heat that's required in order to create these by-products, and say you can't have a product that goes past that heat level.

There are simple ways to make this product available and make the testing affordable and keep it accessible to people who smoke cigarettes that are killing them, so I'm just asking to please reconsider a better way to regulate this product and regulate ingredients and safety and battery safety and UL listing for battery products without demolishing an industry. And that's pretty much what I had to say. Thank you.

MS. JOHNSON: Thank you, Spike. I'll give you guys first crack. Have you had anything to add or --

MR. GRAHAM: I guess I would just add

as I was coming closed in my earlier comments, I do believe that through personal experience that meetings with FDA are really very informative and shining a path forward for such programs and studies.

And you know we heard yesterday how it's important to be thoroughly prepared in these kinds of meetings and not to ask FDA to provide the guidance that's already available and for written, but to do ones homework and really look between the lines of what's been guided already in public.

And therein lies your uncertainty and to go to the agency with proposals for their review and consideration, and I personally have benefited from quite a lot of learning and experience from that, and I think people are really genuinely there to try to help.

MR. NEWMAN: Thank you. I have nothing directly to add to the ENDS topic, other than we feel like we are in the same boat and we would like to work with the agency and figure out

our historic industry can work within the regulations.

MS. JOHNSON: Thank you. Anyone else? Come on this is, like, exciting stuff, right? We all have our armor on at CTPU -- we waiting to hear from you all about this newly deemed products. There's so much in the media. You all have so much information and opinions. Come and share with us.

So when you get up to the mic, just remind us of your name and the company that you're with, please.

MS. HAYDEN: Debbie Hayden, and I had a question from really, from maybe earlier in the day the other presentations that had to do with the cigars since those are also newly deemed, and the discussion about stability testing, and it kind of pointed right at smokeless, which made me wonder is there an expectation of stability testing for the cigars because it made me think maybe there isn't a lot of discussion about what's should that stability testing look like,

so if anybody from the FDA has a thought on that, it'd be helpful.

MR. NEWMAN: While they confer, maybe I can just say that we share your concerns. I was taking lots of notes during the stability testing section just because we know that this cigar has eight year old tobacco in it, and we know that it was rolled last year, and we know that if it ages five years it will taste different than it does now, just like wines or scotch or distilled spirits.

And also know that if I let the cigar outside it's going to dry out and the moisture content will change and it really worries us about this type of testing.

MS. JOHNSON: So we're going to take that back and take that under advisement. Appreciate you bringing that to our attention. Thank you, Debbie.

So what did you all have to eat for lunch? You're so quiet. This morning you were, like, whoa. Now, you're so quiet. Okay. So I

know you're still alive because you laughed at my dumb joke. Great. Don't forget to tell us your name and your affiliation, please.

MR. BECKER: My name is Don Becker and I'm with Turning Point Brands. And the question that I had is I realize that these reviews are to be considered on a case-by-case basis for different products, but there are so many different products out there. And as Mr. Newman explained it's impossible to create such a burden upon industry to have hundreds of thousands of combinations per company.

In some cases you can have a million plus combinations for a single company, and I'm just thinking in other areas of Government, including payment of income tax. You know, the IRS doesn't say, here are the things you might want to consider.

At the very least they do provide some better guidance in terms of a tax form. Fill in these sections. And I'm thinking for SEs and exemption request and things like that, it really

should be able to be reduced to a form. And some things may not apply, there may be a supplemental form. It just seems to be a natural progression to have some things improved so that expedited review of SEs and exemption requests, and even parts of the PMTA to be supplemented with custom studies and things like that were appropriate for the protection of the public health.

But sometimes it feels like some circular references to consult the guidance and these are the things to consider and don't forget to consider and FDA would recommend, but that's not helpful in us in determining how much it's going to cost, how much time is involved, how many people are getting involved.

We start to consider which SKUs we're going to carry in a few years and I'm just looking for maybe some better guidance in that regard. Is something else coming to help us to be more clear? This is a great start by the way, but just looking for something.

MR. NEWMAN: I completely agree. The

idea of an income tax like form with instructions can be really helpful. You know as Thomas was saying earlier when he was up here the technology involved in making one of these is a ruler and a table, and a knife.

And because of that in our industry there are so low bearers to entry there are dozens and dozens of tiny little companies and if we are in the -- at the process or completing of SE and HPHC testing involves consultants and complex forms and everything. It's going to be the five of us in the handmade cigars industry from the back of the room left and all of these small businesses that have been around for a long time are not going to be able to compete and the market is going to get squeezed.

MS. JOHNSON: Thank you. David, anything to add?

MR. GRAHAM: No.

MS. JOHNSON: No. All right. Further?

MR. ANTON: Good afternoon. My name is Mark Anton. I'm the Executive Director of the

Smoke Free Alternatives Trade Association and we represent a lot of small businesses in this vapor category.

And one of the things I wanted to ask is with all of these standards, proposals, directions, guidance, how is a small business person supposed to actually do these things when we see over three million submissions for SKUs for different flavors, for different PG/VG ratios? And if the FDA, when they deemed this, they said this would cost about $300,000, well that's over $900 billion dollars and a market segment about five billion.

So how is a small industry supposed to stay in business? You've got vape stores. I mean, Spike, she's had her store for years. Those folks are the front lines. They're the ones who are helping the smoker understand the complexities of the products and the deliverables to help them to transition.

How is a business like that supposed to stay in business when they potentially won't

have products to sell? Thank you very much.

MS. JOHNSON: Comments from the panelist? Those are very good points.

MR. GRAHAM: Again, I think the question is really leveled to FDA, and I think FDA positions itself to be able to respond to uncertainty of this sort, and I would encourage colleagues in the industry to make best outreach to the agency.

I think if that's not fruitful then it's even more frustrating, but personally, I haven't seen evidence of that, and I think all I could comment on is to use every available resources there including that that's not written such as what FDA is willing to offer.

MS. JOHNSON: Thank you.

MR. NEWMAN: The only thing that I'll add is think about handmade cigars and think about the cost of compliance with SE, HPHC testing and so forth.

It makes me wonder what the cost benefit analysis really is. Particular with our

products are used and frequently bought by adults and whether the high cost of compliance so far is a good efficient use of Government resources and/or there's a better way to achieve the same result, the same benefits, but in a way that allows the industry to continue.

MS. JOHNSON: Thank you. Any other comments? Any further comments?

(Off microphone comments.)

PARTICIPANT: Regards to cigars, there are standardized methods out for cigarettes of Canada (Phonetic) and iso-smoking regimes, for example, but there are no clear guidelines for cigars, and what to do. There are also no reference products. I was hoping you could provide some comments on that as the FDA. And, whether to follow the CORESTA recommended methods which are continually changing and are in review now or going to isolate.

MR. NEWMAN: That's a great point. It worries us, like, on the cigarette side there's a well-developed testing regime. There are standard

sizes and those sizes have billions and billions of units. There are a thousand different sizes of cigars.

This is a Toro at about six inches long. This is a Corona it's shorter, it's thinner. This is a Robusto. These are three of about a thousand sizes in the same brand family, and we're looking to CORESTA in the international community to help us think about the testing regimes.

But how you create a scientific standard for wide variety -- products that come in a wide-variety of sizes and it's a challenge. And there's also research showing too that consumers consume different cigars in different quantities. Some will smoke the entire thing, the other will put it down after a quarter of an inch, or half an inch.

So trying to create something that's realistic and achievable and is cost effective when we're dealing with such low volume quantities and products is a real challenge and it worries

us.

(Off microphone comments.)

PARTICIPANT: Thank you. And also, a follow up question. Could you comment of machine made cigars which are still basketed with products like cigarettes? Do you have comments on that? And, how to test those as well?

MR. NEWMAN: Sure. Well, when I think of testing in machine-made products there was a study that came out and I believe the nicotine and tobacco research journal about a year ago, and it was done by some FDA colleagues over there who bought a set of cigars in 2015.

Bought the same cigars on market in 2016 and did a host of test on them and they found wide ranges of differences in nicotine and other HPHC from one year to the next just given the natural variations.

I think most of those products were machine-made. There was a Monte Cristo cigar, handmade cigar in that cohort too, but it just suggest to me that our products really are subject

the natural variations of nature, and so trying to apply a strict scientific regime to a product that is inherently natural and handcrafted is a real challenge.

MS. JOHNSON: Thank you. Any other comments or thoughts, or observations? Okay.

Well, let's thank our panelist David and Drew. Appreciate you coming. Thank you so much. And now, I will turn it over to Dr. Holman to kind of bring these two days together and wrap everything up.

MR. HOLMAN: So before Joe and I present our closing remarks, what I'd like to do since we have some extra time -- where did the microphone go? If we can get the microphone back.

I mean, one of the things you'll hear in my closing remarks, and hopefully, you picked up yesterday in the opening remarks is, you know, we put on this two-day meeting as a way to dialogue with stake holders we hope in a productive effective way.

We debated the format, how to do this,

how to best accomplish that goal of having that dialogue, and I think it would be useful to hear from participants, attendees in the room. If you're comfortable stepping to the microphone, just sort of sharing, you know, how well this meeting worked or didn't work and just give us some honest feedback.

I've asked Joe if he wouldn't mind sort of kicking off that discussion with his own observations, which he's agreed to, but after Joe is finished speaking on that if others feel like they want to come up to the microphone, we're happy to take that feedback.

So do you want to do it from there?

MR. MURILLO: Yes. This is fine. Am I on? Yes?

MR. HOLMAN: Yes, it's green.

MR. MURILLO: Okay. So thank you, Matt. I'm Joe Murillo, Senior Vice President of Regulatory Affairs for Altria. As most of you know Altria is a holding company. We own a series of tobacco companies including Philip Morris USA,

U.S. Smokeless, Matt Sherman, John Middleton, and Nu Mark.

I will tell you that first I will add my thanks to tell Matt and to the FDA for putting this together. I will also tell you that in terms of the dialogue this is one of the first times that I really felt acknowledgment from the agency as our regulator for some of the issues that we've been facing, almost in some cases empathy, and I have to say goes a long way. At least we're hearing each-other. You're hearing that we have some questions, we have some frustrations, we have some issues, and that helps.

You acknowledge that we need rules. You've acknowledged that there's been some evolution. You have acknowledge that there are some difficulties remaining. You've acknowledged that everybody would like there to be better dialogue.

The second thing that I would say that we should remember that we are unique in this area and in this country for having this inclusive

approach to regulatory proceedings and dialogue. I've been with Altria for more years than I'm going to mention right now, but before this assignment I've had other assignments where I've dealt with regulators abroad and there is not this sort of dialogue that I can think of just about anywhere.

In terms of the feedback and the most effective exchanges, I think that exchanges that assumed basic knowledge were more productive. So in other words, if we ask a question that is carefully worded within the terms of the statute and the guidance, and you answer the question with carefully worded language that recites back to me what I already know that's in the guidance that is not a useful exchange to either one of us, right.

So I think the flip side is you have to come prepared. The regulator should be entitled to assume or tell us that they will assume, that they will assume basic knowledge of what's already in their statute and the guidance, and if people have scoured the website to find every last bit of

feedback that is available, and then you can ask a more insightful or relevant question.

In that regard, I thought that one of the things that worked particularly well yesterday and today is the level of detail in examples that were provided by the agency. I think the detail in examples we got yesterday with respect to the SC process was terrific. It, for us, confirmed some things we've been seeing in recent letters. In some other cases it caused us to sort of ask around, hey, did you see that, is that what they meant? And I think that was very helpful.

Dialogues that are two-way that allow for Q&A are the best. Because of unfortunate circumstances we couldn't have that in this very last session that we just went through, but with that as an exception because of the circumstances, I think situations like this where I can be sitting in a room with some of the people who only know me because I sign letters or I only know them because they sign letters back to me is very helpful.

I think with that level of detail an improvement would be maybe starting to tiptoe toward areas, new areas, where we can apply these learnings and observations to future issues, right. So can we be comfortable, can we become comfortable starting to talk about how will we think about HPHC for cigars. What will we do with analytical variability? Are there some parameters that we might think about with respect to design issues?

I mean, I was listening to Mr. Newman. I have no idea how we're going to get certificates of acceptance, etc., etc. for design parameters for cigars in the premium area.

Same with vapor and I think we heard some useful beginnings of conversations with respect to HPHC and also some, I think evolutionary dialogue with respect to the very serious youth issue. Dr. Gottlieb has talked about the youth epidemic. I don't see how we're going to be able to achieve PMTAs for some of these products without more directly addressing

the potential for youth appeal.

Other feedback that I have written down is that you ought to make sure you're posting some of this information in real time. So we talked about things that, you know, we got in FOIA or someone else has gotten. We talked about the attachment that is going with SC letters, etc., etc. If there are memos that people can get through FOIA in any event or things that you are sharing at a conference, why not post it? Maybe even post before the conference so we can study it and come with deeper questions.

We talked a little bit about a different way of communication which is potential dialogues during the review process. And I understand the difficulty with having deep conversation in the review process, however, clarifying questions are not always the most effective. I mean, we've used them but it kind of -- I suspect leaves both sides hanging sometimes saying, gee, if I could only ask the applicant of a follow-up and that may save me 40 hours of work

or something, and maybe there's a little bit more that could be done there.

And then my final suggestion in terms of feedback would be workshops like this and workshops of this nature on specific topics.

So for example, we started to touch on population effect issues and post market surveillance and youth appeal issues. These are very thorny topics and we don't have a lot of history yet in the PMTA program, in fact, we have precious little to be able to draw conclusions or draw examples from that. Maybe a format could be developed where both sides could be comfortable having some sort of workshop type dialogue on more specific issues that are relevant to applicants and reviewers. So those are some thoughts.

MR. HOLMAN: Great. Thank you. If others want to step up the microphone and share any of their thoughts, we'd be glad to listen.

Again, please state your name and your affiliation for the transcriber.

MS. BABAIAN: Spike Babaian. New York

State Vapor Association. I liked your thought on topic specific meetings. It might be helpful to potentially letting the vapor industry survive if there were discussion of testing methods that we could use since there aren't standardized testing methods yet, and maybe putting together something on how we can assess different things that affect us.

Environmental assessment for vapor products that don't have side streams smoke and don't have -- you know, there are a whole different realm of tests for us that are going to be required. And I think there is a potential for more companies to maybe make it through if they're working together to use, you know, bridging research if we can get together to do that. And with the FDA's help that might be a possibility, so that would be appreciated.

MR. HOLMAN: So just to wrap things up. First I want to thank all of my colleagues in the back of the room and those that are aware in the hallway for doing a lot of prep work to make this

meeting happen, doing a lot of behind scene work yesterday and today to make sure that the meeting goes on as planned, so big thanks to them.

I would also like to thank all of my colleagues who gave presentations of the last two days. I particularly thank those that sat on the panels and took some, I think some good, honest feedback. And so, again, thank you guys for your participation in making this meeting a success.

I would also like to thank the panelist for be willing to sit up here and be candid and share their perspectives, share their concerns with us, and so, that we can have a productive conversation and dialogue about some of these issues, so.

And then lastly, thank all of the participants both of those in the room as well as those viewing remotely for all the questions. Obviously, those questions generate a lot of good discussion and brought out a number of issues that otherwise would not have been brought out, so again thanks for everyone for active engagement in

this meeting in order to make it as successful as it could be.

In terms of goals we had for this meeting coming into it, you know, the goals I jotted down as I was listening for the last couple of days thinking, you know, what do we set out to do and how well do we do it. I think we actually, in my mind at least, personally I view this as a very successful dialogue over the last two days.

As you guys heard over a little bit, over a year ago Commissioner Gottlieb asked us to really assess, evaluate our application review programs. We certainly had been doing that in this meeting as it was meant as a way to bring to light. I think to make more public some of the things we've been doing to really assess our application review programs to determine how we could maybe operate in more efficiently and effectively in evaluating applications.

So some of the specific goals are that we wanted to share information that we hoped would be useful to stake holders ranging from those

companies who have not yet submitted a marketing application, which we heard from just a moment ago to those who maybe have extensive experience and have submitted numerous applications to us, and have interact with us in a variety ways. And so we hope that there's information really for all the manufacturers from the small to the big that you found useful over the last two days.

Another goal that we sat out to achieve that I think we did a good job of is really just laying out for you guys sort of the evolution of our programs over time. Obviously, the SC and EX have evolved much more than PMTA at this point because we've got a lot more experience both at our end and at the applicant's end, and those two programs.

And we've also heard a lot of feedback over the years about those programs because of the experience. And hopefully, what you've seen today or heard today and yesterday that is that we do listen, we do hear these things and we do try to have the programs evolve in a very positive way

based on those experiences and our own direct observations as well as what we hear from other stake holders about the programs.

And then lastly, we were really hoping for a conversation. We were looking at this as an opportunity to solicit feedback and ideas for places where we could improve for ideas of how we could improve in some of our programs and further evolve them. I think what made it successful discussion or conversation from my perspective is, you know, I thought it was a very balance, fair, perspective shared by all participants. A very respectful tone to the conversation, which I think it is imperative because it doesn't always exist in all forums.

And also, the candidness, I think we can only learn as much as what's shared with us and I think folks willing to be candid and share their perspectives, share some of their concerns and the reality that they're dealing with is very helpful to us. So I do appreciate that.

I heard a lot of things over the last

couple of days so I want to note some of the feedback I heard and particularly some of the things that really got my attention, but I figured it would be funner for you guys to guess what got my attention, so I'm going to leave it at that. Any guesses Joe?

No, all in seriousness, I mean, I was jotting notes the whole day, yesterday and today on a lot of good feedback and a lot of good ideas. I'm just going to capture a few of them and share some of my thoughts or provide, maybe in some cases more information.

On one of things that was talked about a lot of the last two days are industry meetings. I think one of the realizations that I've had recently is that maybe our message about industry meetings and our advice to applicant's to be very thoughtful and careful about when they submit, how many they submit. Maybe that message went a little too far. And maybe folks aren't utilizing those pre-submission meetings to the extent that they can, and so I just want to encourage folks.

You heard David Graham, for example, in the last session talk about how useful they can be. I think they are a great tool that maybe is being underutilized and maybe that's partly our fault for the messaging around those industry meetings. But I would certainly encourage you to submit meetings before you submit your applications.

But also I would say be thoughtful about the topics and how you frame those meetings because they are only successful as -- they are only going to be as helpful to you as based on how well you ask the questions that you need to ask of us. And I think we've seen, internally, as we do these -- that some of those I think we view as very productive for the applicant. I think other times we review them probably is not all that helpful to the applicant, and that's really based a lot upon the questions that get asked of us and information that gets shared with us.

As an example, we sometimes get asked, like, here's my whole plan for submitting a PMTA,

will this get me a marketing order? Can't tell you that, right. But on the other hand we get other very specific questions, like, you know, here's the clinical studies that we think might possibly support our market, you know, marketing order under these applications, do you have any concerns with the study design, the study size, anything like that? Very specific questions where we can say, no, we don't have any concerns that looks like a study design that might work. Or we might say, yes, we do have concerns we think it's under powered or something along those lines.

So again, as you think about submitting meeting requests just be very careful about, you know, what you're asking and make sure you really get out of that meeting what you're hoping to get out of it.

Another area that we certainly heard over and over again is just more regular and improved communication with applicants. You know, today is part of that, but we need to do more, we're trying to do more, we're trying to utilize

the website in better ways. I think we heard some good ideas, some good comments about the content.

For example, yesterday and how easy or difficult it might be to find some of the information on the website, but there are a lot of tools that we can use to communicate. This meeting today and yesterday is one of those tools, but there were other variety of other tools that, you know, were exploring how to best utilize them to improve communication beyond where we are today.

And then lastly, another issue that came up yesterday was just talking about and today, talking about electronic submissions. You know, we view that as a tool to help applicants to make submission to us easier than it could be, but we're also hearing that sometimes that there are challenges there that we need to try to work on tackling. But we did hear that there is some interests or some companies that are following the CDT model for their applications and heard that, that seems to work well.

So again, we're going to take that back and figure out what we can do with that and how we can facilitate electronic submission of the applications.

So just to wrap things up, again I think this is, in my view, was a pretty successful meeting. I hope all of you feel the same as well.

And again, as I said earlier, I think that all goes to active participation by all attendees and not just, you know, FDA up here speaking. I think we saw that it was very helpful to hear all of those perspectives.

Also would remind you that the docket is open and it will stay open after this meeting, and so if there is additional thoughts or ideas that you didn't get to share or that came to you during the meeting, but you didn't have the opportunity to share them with us, certainly, submit those to the docket. We will be evaluating all those docket submissions after the meeting.

Our slides will be made available that we presented over the last few days. They will be

made available on the website, hopefully, shortly after the meeting.

And we hope to walk away from this, again, with some ideas about how to better create a dialogue going forward. You know, we hope this is just not a one-time dialogue. That there are ways we can maybe do things like Joe suggested where we pick specific topics and have these types of conversations around those topics.

So thank you all for your time. Thanks for sticking around over the two days and engaging really in the discussions here during this meeting, so appreciate it.

MR. MURILLO: So thank you, Matt and thank you for the opportunity to giving some closing remarks from a regularity perspective.

Let me just say first that I would feel reminisce if I didn't acknowledge the sad news that Mitch shared with us yesterday to start the meeting, and that is about the untimely passing of David Keith.

David was a dedicated and able public

servant and those who have worked with him found him to be approachable and collaborative. So on behalf of all of us at Altria we send out condolences is David's family and his many colleagues at CTP and across FDA.

Now, turning to this event, I want to add my thanks to the agency for hosting the workshop. I'm encouraged by the open and transparent conversations among the presenters and panelist.

This is really important communication, and in fact, we think a cornerstone of a successful framework is effective, open and ongoing communication.

And in the announcement for the meeting Dr. Gottlieb stated that establishing a rigorous predictable science based framework for the pre-marker review of tobacco products is a key element of our program.

Moreover, today and yesterday we heard a lot about CTPs desire for consistency, transparency, and predictability and that is, of

course, music to our ears.

I think this public workshop represents a great step in advancing these initiatives. Not only did it provide a forum for stake holders to engage in collaborative and transparent fashion, but also allowed the agency to hear direct feedback on how to improve and potentially evolve the framework.

This brings us back to the purpose of the workshop to share of experiences, learn from others, and hopefully, to contribute to a better regulatory process and to foster innovation. We all need to be on the same page regarding the rules of the road. This much we seem to be agreement on, and I'm going to take my own advice and not tell you what you've heard me and my colleagues say many times, which is that it's hard to do that when the rules are not written down or the subject of notice in comment rule making, and I will move on without telling you the content that we believe is necessary because you've heard it before.

So in closing, I would tell you that we encourage CTP to have more sessions like these and other less formal exchanges where we can come together and compare learnings, and exchange actionable ideas in an appropriate way.

I think we can work together, communicate effectively, and work to implement the pathways that we've been given, particularly, to allow innovated products that can reduce the harm caused by tobacco to come to market and improve the public health. Thank you very much. See you soon.

MR. HOLMAN: Thank you everyone. Safe travels.

(Whereupon, the above-entitled manner went off the record at 2:43 p.m.)

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C E R T I F I C A T E

This is to certify that the foregoing transcript

In the matter of: Tobacco Product Application Review

Before: US FDA

Date: 10-23-18

Place: Rockville, Maryland

was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

Neal R Gross

Court Reporter