FOOD AND DRUG ADMINISTRATION (FDA)

Center for Tobacco Products (CTP)

Roundtable on Premarket Tobacco Application Submissions for Electronic Nicotine Delivery Systems Products

February 10, 2026

TRANSCRIPT

This transcript has not been edited or corrected but appears as received from the commercial transcribing service.

[music playing]

Matthew Farrelly:
There we go. Good morning, everyone.

Male Speaker:
Good morning.

Matthew Farrelly:
I'm Matthew Farrelly. I'm the director of the Office of Science at the Center for Tobacco Products. Welcome to today's roundtable discussion on premarket tobacco product applications. I'm pleased to see you all here on—you know, so we can all work together and review the PMTA process together. And I also just want to thank you for taking the time out of your schedules to be with us and share your experiences.

We will have five panel discussions on topics that include product characterization, manufacturing controls, pharmacological profile, studies of adult benefit, and toxicological profile. We will include three breaks, one in the morning, one for lunch, and one in the afternoon. And we'll wrap up at 5 o'clock.

The purpose of today's roundtable is—there's two purposes. First, we want to provide you with comprehensive insights into the scientific evidence FDA needs to evaluate whether a tobacco product is appropriate for the protection of public health or APPH. Our expert presenters—sorry, our expert presenters from the Center for Tobacco Products will walk you through the critical components of a successful PMTA submission, with particular focus on ENDS products.

Second, and equally important, is we're here to listen to you. We recognize that small manufacturers face unique challenges in navigating the PMTA process, and your experiences and perspectives are invaluable to us. Throughout today's session, we will be soliciting your feedback on the review process, what's working, where you're encountering obstacles, and how

we can better support your efforts to bring compliant products to market.

We want to know if you have had—if you have the information that you need to be successful in this process and what you need to do to navigate successfully. This is a conversation; it's not a presentation. And your input will help inform how we can improve the process moving forward.

I want to say a little bit more about what we're going to cover before we kick it off. So, we'll start with product characterization and manufacturing controls. We'll begin with the fundamentals, understanding your product's physical properties, composition, and design specifications, followed by the manufacturing processes that ensure product consistency. Next, we'll talk about the pharmacological profile. Our team will discuss how we evaluate abuse liability and addiction potential through clinical studies, including study design considerations and product bridging approaches.

Next, studies of adult benefit for flavored ENDS products specifically, we'll outline the evidence needed to demonstrate added adult benefit for smokers that can outweigh the well-established risk to youth. And then finally, we'll talk about the toxicological profile. You'll learn about our risk assessment framework for both cancer and noncancer hazards, including how product design choices directly impact toxicological risk.

So, our goal today is not just to explain what we require, but to help you understand why these requirements matter to public health protection. For each presentation, we will include practical examples, common issues we encounter in applications, and resources to support your submission development.

More importantly, we want to hear from you about your real-world experiences with these requirements. What challenges have you faced? Where do you need additional clarity or support? Your candid feedback will help us identify opportunities to streamline processes, improve guidance documents, and provide more effective technical assistance, particularly for small manufacturers.

We encourage you to take notes and prepare questions for our panel discussion. We also welcome your suggestions and constructive feedback throughout the day. Thank you for your commitment to submitting high-quality applications, for taking the time to share your experiences with us, and once again, welcome and let's begin.

All right. Todd, are you next?

Todd Cecil:
Good morning, everyone. Thank you, Matthew, I appreciate it. I have the great pleasure to moderate a few sessions today. To give you a sense of the structure of what we are going to do here today, I want to first describe to you the agenda of this first session and those that will follow.

Each session will begin with a brief presentation of information from FDA, and I'll introduce our speaker momentarily. And we're going to talk about what does FDA use when we do evaluate

APPH for ENDS products. These presentations are not intended to cover everything that is considered or how decisions are made but instead are intended to present a brief primer on the topic so we'll all be on the same level playing field when we begin our discussions.

These are scientific topics that deal with what FDA considers during the review process. We are the Office of Science after all. We will not be discussing logistics of a submission, the timing of the submission, the specifics of any applications that are pending or that you are in the process of putting together. These presentations are intended to be brief, about 20 minutes in length.

After the presentation, I will introduce the participants in the roundtable. I will ask each participant to give no more than 2-minute briefing on who they—who you are, who you represent, and some information about how you are an expert in this field and give a brief introduction.

The discussion will be limited to individuals in the roundtable and may involve the moderator offering questions on certain topics to spark discussions. I prefer not to have to do that. So if you all have topics, please jump in whenever you can. These topics may be taken from questions submitted to the docket. We have considered all of the information considered to the docket. That docket remains open and additional information and suggestions can be submitted to it.

The moderator will be expected to intercede if discussions go off topic. I hate talking about myself in the third person, but I will not be the moderator for the entire session. So, we will try to move the discussion along and—if we've already—we're covering ground that's already been covered. However, at the end of the day, our goal is to answer those questions that we can and to listen to the stakeholders on the panel to understand the difficulties that small businesses may need to overcome and, hopefully, ideas on ways to reduce those difficulties.

You are welcome as panelists to talk to the individuals between sessions, that may be sitting in the audience. However, we will not be accepting questions from the audience.

All right. So, our first session pertains to the topic of product characterization, one of nearest and dearest to my heart. Product characterization relates to the number of foundational pieces of information that we rely upon to define what a product is, what a product is made from, what the product is designed to do or deliver, and what a product actually delivers. These questions define, support, and inform discussions and considerations for the toxicological profile, the pharmacological profile, and to some degree, the epidemiological profile of your products.

We will in due course of the day discuss critical attributes of each of those areas as a scientific consideration. So, we begin this discussion with a presentation of what our reviewers are looking for with respect to product characterization information. Our first presenter is Commander Walter—Walter Matthau—Matthew Walters. He's actually quite funny, so it works.

Matt has been with the Center of Tobacco Products in the Office of Science since the very beginning. He started his tenure with us in 2010 and has been involved as a chemistry reviewer, branch chief, and now as a Deputy Director of the Division of Product Science. Commander Walters has extensive experience in reviewing PMTA applications and the needs of product

characterization in these reviews. So, let me turn the floor over to Matt. Thank you.

Matthew Walters:
Thank you, Dr. Cecil, for the introduction. Good morning, everyone. My name is Commander Matthew Walters, and I'm the Deputy Director in the Division of Product Science within the Office of Science at the FDA Center for Tobacco Products. Today, I'll walk you through the critical elements of product categorization that FDA needs to evaluate whether a tobacco product is appropriate for the protection of public health.

Complete product characterization is crucial for complete PMTA, as, for example, the incomplete or lack of full list of ingredients and the information supporting harmful and potentially harmful constituent measurements prevents the complete assessment of the toxicological risks of a product.

Furthermore, the lack of comprehensive methods for nicotine content and [unintelligible], where appropriate, means that we cannot fully evaluate the abuse liability and nicotine exposure of the product. These are just a few examples of the importance of product categorization to understand your product and support the decision-making in determining whether your product is appropriate for the protection of public health.

Product categorization is the foundation of any PMTA. We need complete information about your product's physical properties, composition, and design. This includes design specifications, ingredients, HPHCs, and product stability. Let me first start with design specifications. Your application must include a comprehensive table listing all design components. This should identify every component and material such as the batteries, heating elements, everything that comprises your product.

For each component, provide target design specifications with upper and lower range limits and most importantly, measure test data demonstrating these specifications are met throughout the manufacturing process. We need to see that what is in your design specification aligns with what you are manufacturing.

Moving to ingredients, we need a complete listing of all single and complex ingredients. For each ingredient, provide the IUPAC or common name, CAS number, purity and grade, supplier, and function. Provide information on which component contains each ingredient and provide the target quantities with acceptable ranges.

For complex ingredients with flavor formulations, tobacco product master files are an excellent avenue for providing proprietary information to FDA while maintaining confidentiality. FDA previously discussed the use of tobacco product master files in previous workshops, with FDA last discussing this topic extensively in October 2023, and I encourage you to review those materials.

Nicotine deserves special attention. We need detailed information about your nicotine source, including a form, whether it's a salt or unprotonated, the specific form name, and critically, whether it's tobacco derived or non-tobacco nicotine. Provide the target quantities in acceptable

ranges and appropriate units for the nicotine. For non-tobacco nicotine, FDA also needs information on the enantiomeric purity for scientific review of the PMTA.

Harmful and potentially harmful constituents are crucial for our public health assessment. Your PMTA must include measured HPHCs with constituent names, means, standard deviations, and number of replicates. Specify the emission regimen used and provide comparison to other products on the market, both cigarettes and FDA-authorized ENDS products where applicable. These comparisons are crucial in weighing evidence for appropriate protection of public health decisions.

Product stability by both microbial and chemical must be demonstrated throughout your proposed shelf life. We need measurements at the beginning, middle, and end of shelf life for water activity, total aerobic microbial count, yeast and mold counts, and tobacco-specific nitrosamine, including NNN, NNK, and total TSNAs. For certain products such as ENDS, we also suggest beta-glucan and endotoxin testing.

Providing preservative identification in quantities would also be important in determining product stability. Similarly, we would need—we would be interested in stability of select chemicals such as nicotine, nicotine degradants, and other chemicals over the shelf life of the product. These measurements are needed for FDA to assess the potential health risks of exposing users to microbes, HPHCs, or toxins that could emerge when the product sits during storage.

While we just discussed the critical aspects for product categorization of any PMTA such as design specifications, ingredients, harmful/potential harmful constituents, and product stability, there are other considerations that are helpful in characterizing your product's physical properties, composition, and design. These include information on the chemical and microbial testing procedures, leachables and extractables, and information to support bridging of a product that is not your intended new product. These will be discussed further in the next few slides.

Product characterization data and associated testing requires validated methods. FDA is seeking confirmation that the method is fit for purpose for the matrix as well as the intended analyte parameter. Ideally, when possible, the validated method procedures should be conducted relative to a reference product that is similar to the product that is tested. We look at four major parameters: accuracy, precision, selectivity, and sensitivity. However, we consider the entire validation procedure report in determining whether the method is fit for purpose.

Specifically, we describe accuracy as the closeness of the mean test results obtained by the analytical method to the true value of the analyte. For example, a method measuring nicotine and cigarette tobacco fill provides a result of 13.5 mg/g when a hypothetical tobacco product reference standard value is 15 mg/g, demonstrating that the method accurately measures the nicotine content.

Precision is the closeness of individual measurements of an analyte when the procedure is applied repeatedly to multiple aliquots of a single, homogeneous solution of an analyte. For example, if you test 10 replicates of menthol in the same cigarette sample that is a mean—that has a mean of 5 mgs per cigarette and the measurement ranges between 4.2 and 5.8 mgs per

cigarette, this shows that the method produces consistent reproducible results.

Selectivity is the ability of an analytical method to differentiate and quantify the analyte of interest in the presence of other matrix components present in the sample. For example, an accuracy measurement—sorry, for example, a selective high pressure liquid chromatography method for NNN and smokeless tobacco would accurately measure only NNN without interference from other TSNAs such as NNK, NNT, NNB, nicotine, or tobacco matrix components like sugars and humectants.

And finally, sensitivity is the limit of quantification, or LOQ, and the limit of detection, or LOD, of the method. For example, hypothetical method for measuring formaldehyde in ENDS aerosol may have an LOD of 0.03 microgram per ml and an LOQ of 0.09 microgram per ml, enabling detection and quantification of this harmful constituent load levels in aerosol. Very technical, so.

Method verification, a few thoughts on method verification. A validated method can be extended to other products within the same category through a verification process. Verification is a demonstration of a laboratory's ability to successfully meet performance criteria established for an analytical test method previously validated in the laboratory performing the validation. Any substantial changes to a method result in a new method should be independently validated.

Common issues we have seen include deviations from standard methods that aren't explained, inappropriate reference standards, inadequate replicates, and methods not validated for the specific product matrix under review. We strongly encourage you to consult our newly finalized Guidance on Validation and Verification of Analytical Test methods released in January 2025.

For ENDS products specifically, we're concerned that constituents that may leach from components in direct contact with the e-liquid. The potential harm from leachables in organic e-liquids is less well understood than aqueous medical products making product-specific studies essential. Materials in the container closure system can produce potentially hazardous constituents. Certain plastics can release antimony, which is why leachable studies on the container closure system may also be needed.

Extractable studies during the design phase can help you avoid components that leach harmful constituents. These studies also help identify targets for your leachable studies, which often have more complicated data. Confirming the identification of every constituent may be quite challenging; however, provide as much identifying information as possible and how each constituent may impact the risks of using the product.

The need for leachable extractable data in studies is product class specific based on the characteristics of the product. These types of studies may not always be needed for all types of tobacco products submitted under a PMTA.

When appropriate, bridging data can be used to characterize your product, but you must provide scientific rationale. Bridged products should be represented—representative and measured under the same conditions, same shelf life, same container closure system. For example, HPHC data from a prototype product might be bridged if you can demonstrate similarity to your new

product. It should be noted that I'm referring to the use of bridging data in the context of product characterization only. The applicability of bridging data for other parts of your PMTA may vary and depends on the specifics of your application. The use of bridging data is not a one size fits all.

Let me conclude with some essential takeaways. FDA needs complete product identifying information to understand your product's physical properties. This is the crucial first step in our decision-making process. All test methods must be validated for your specific product type. Tobacco product master files are valuable tools, especially for proprietary complex ingredients and analytical methods.

Most importantly, tell your story to FDA. Help us understand the complete physical characterization and composition of your product. We have several helpful resources available including updated guidance documents and posted FDA memos on the evaluation of extractables and leachables.

Provided in this slide are some additional resources which provide further information on some of the topics that were just covered, including the guidance for industry on listing of ingredients in tobacco products, guidance for industry on premarket tobacco product applications, and the guidance for validation and verification of analytical test methods, as well as posted FDA memos on evaluation of extractables and leachables. These resources are available on FDA's website. We encourage you to construct—consult them as you prepare your application.

Thank you for your attention. Product characterization is fundamental for FDA to understand the crucial properties of your product.

Todd Cecil:
Thank you, Matt. Now, we can get into the whole point of the discussion and actually have a discussion. And we're going to start by doing introductions. I have proven thus far that I am terrible at reading aloud. My children will attest to this. So, I'm going to ask each individual to introduce yourselves. We're going to begin—and there's a longer list here. You can read through. It's in your packet that has the background for everybody. But I'm going to start all the way at my left-hand side and move to the right. So, let me start with Dr. Colleen Rogers.

Colleen Rogers:
Good morning. I'm Colleen Rogers. I'm the Director of the Division of Product Science in the Office of Science. And Division of Product Science staff are the ones responsible for reviewing the product characterization and manufacturing parts of the applications.

Matthew Walters:
I'm still Commander Matt Walters. I am—as I mentioned, I'm the Deputy Director in the Division of Product Science, and I oversee the chemistry discipline, mainly.

Karen Coyne:
Good morning. I'm Dr. Karen Coyne, the Associate Director of the Division of Product Science, and I'm an engineer.

Todd Cecil:
Mark.

Mark Anton:
Mark Anton, CEO of What A Smoke, been in the business since 2008, and have been engaged in NIDA contracts as well as development of pulmonary delivery devices.

Geoff Habicht:
Good morning. Thank you for having us. My name is Geoff Habicht. I'm the co-founder and president of Mi-One brands. I have a background in engineering. We've been in the business since 2008 as well. And I just wanted to take a brief moment to say we have an aligned mission, the FDA, the TCA, and us as small manufacturers, which is to eliminate the harm caused by cigarettes. It's been a mission that most of us that are small manufacturers started our businesses with because we quit smoking. We saw what it did to our families and their lives and our lives. And that mission is aligned. So, we want to comply, we want to go through this process properly, and we need this communication in order to do that. So, thank you.

Ryan Muckenthaler:
Good morning. My name is Ryan Muckenthaler, and I'm a member of Lotus Vaping Technologies. We are a small business manufacturer located in Boise, Idaho. We make American-made e-liquids. We've been in the industry for I guess since 2012. We employ around 275 professionals that support our compliance, manufacture, distribution, and retail operations. As a larger-scale business, we contribute meaningfully to the United States employment and value and quality in the vapor marketplace.

William Tang:
Hello, everyone. I'm William Tang, [unintelligible] ZOOVOO Tech company, and our company is a brand-new company in China, and I'm responsible for the product compliance and PMTA applications. And our company started PMTA submission from 2022. And also, we have submitted more than 20 product submissions. And I think it's a good honor to—opportunity to attend this roundtable.

William Wikstrom:
Hey. Good morning, everyone. I'm Bill Wikstrom. I'm the owner of Vaporized and Paradigm. I've opened my establish back—establishment back in 2013 with a focus on retail and wholesale operations and e-liquid manufacturing in the state of Mississippi. Since 2016, I've been working very closely with legislators to push forward smart, sensible legislation with a focus on youth prevention. And I appreciate the opportunity of being here today to work with the FDA and seize this opportunity in order to see if we can bridge the gap here, find smart, sensible regulations that will help support small business in the industry. Thank you.

Todd Cecil:
Thank you very much. And so, I think we can now open the floor if you all have any opening questions that you'd like to ask or any comments you'd like to make that we can address. If there isn't an opening question, I can go ahead and throw some. Geoff?

Geoff Habicht:
Sure. I can ask an opening question. So, Dr. Makary has often mentioned the need for predictability and transparency from the FDA in terms of regulation. And for small manufacturers like us with limited capital, predictability is critical. Does the FDA agree—well, has the FDA considered defining product characterization benchmarks such as temperature thresholds, emissions, exposure ceilings, that if met, are considered APPH and could provide a more predictable review pathway, and therefore preserving efficiency for the agency to do farther full—fuller reviews on higher risk products that are outside the scope of those benchmarks?

Matthew Walters:
I would say that's a challenge because product characterization is just one aspect of the total consideration of a PMTA in appropriate protection of public health. But as I just went through, there are certain aspects that I would say are crucial to our understanding of that product industry for product categorization. But there are other things that we have to weigh. So, I don't think that as one side or other side. I think it's the entire picture to kind of assess the different aspects of the weight of evidence from the various disciplines to make that decision, so.

Todd Cecil:
And I think I want to add that we will talk about it when we get to each of the—in the afternoon, like each of the afternoon sessions, we'll talk about specific applications of product science and, you know, product characterization, manufacturing control, and how it affects our assessment of APPH. But APPH is not a single defined number. Something can have an elevated level of an HPHC that is of concern, but there may be benefits that can overcome that. So, I—there's no way to say if you have this number, you're APPH, we can look at it and give you some idea. And I think toxicology will present an approach to give you an ability to do some calculations and think about what level of toxicity is being represented by your products. So, we will be talking about that a bit more when we get to the afternoon sessions.

Mark Anton:
Yeah, I have a question. I was noticing in the slides—and obviously, things have progressed farther from when I originally started this process years ago. There shows a—that we need to compare to even products that have been approved. I make hardware. I don't specifically make liquid. So, the gentlemen on this table that make liquid, my device and their liquid would marry up potentially. But I see that now, I'm supposed to do comparisons of HPHC to products that have already been shown to be appropriate for protection of public health. And as a small business manufacturer, I know what NJOY submitted and how extensive and how expensive it was. How is a small business like myself that works in higher powers, more controlled scenarios, supposed to augment my application to include such a larger array of material? Is there—I don't know if there's a tobacco master file for them that I can utilize, but it would seem really redundant and a waste of expenditure for something that's already been ascertained.

Matthew Walters:
Yeah. Those comparisons are in the context of HPHCs, as you mentioned, that I think it's not expected that you would go out and measure those HPHCs of the already authorized ENDS

products. A lot of that is in literature now. And so, I think if you provide that evidence in the PMTA for what the current marketplace HPHCs for authorized ENDS products, that would probably likely be sufficient. It's not that we expect that you go and measure all those HPHCs of all the ENDS products. That's not the expectation there.

Karen Coyne:
If I may add to that, when you're doing that comparison, it helps us to see how the HPHCs compare if you provide a comparison of the design parameters and any differences between your product and the product that was tested. Because if your design parameters are completely disparate, well, it helps if we have the design parameters so that we can do—evaluate the comparison.

Ryan Muckenthaler:
Thank you.

William Wikstrom:
I have a question. Oh, go ahead, please.

Ryan Muckenthaler:
Thank you so much, sir. I appreciate you bringing that up, Mark, because it is definitely—thank you so much—it's definitely a concern of mine as well as an e-liquid manufacturer that, you know, having very little information about the designs and product specifications of his hardware and his hardware, it brings into—I guess a lot of unknowns, a lot of variables. It seems to me that a set of product standards would really eliminate a lot of the unknowns for me. So, is the FDA considering or weighing releasing any product standards for—I guess to solve the issues that we see in the main—or in the PMTA process and in the marketplace so that as an e-liquid manufacturer we can produce products to a certain standard that can be held to that APPH?

Todd Cecil:
I think we need to keep in mind, releasing information is a regulatory function. So, if we are going to say whatever the level of exposure can be, we are limiting the entire marketplace, and therefore, we're going to have to go through either a guidance process—and that's a recommendation of what you might like to see. That can take years. Same with regulation. The other option's the product standard. Product standard can also be done quickly. But again, those—that's a—that's not a "we'd like you to," that's a "you must" do something.

And to certain—this is a very rapidly evolving industry. There's a lot of manufacturers making a lot of different products, many of which are going to be appropriate. And if we set out blindly setting up a standard that is going to impact you negatively, we expect there's going to be lawsuits. We expect there's going to be responses to a—to our product standard, to our guidance that we're going to have to deal with. It just kind of drags the process out.

We try to give out as much information as we can. All we can really do is give guidance to our own staff on what we should be looking for. We try to make that available on the website where we can. There are restrictions to what we can put out, and they are not that we do not want to provide it. There's just restrictions legally that we cannot do some things. There's processes we

must follow. So, you know, we would love to give you lots of guidance, but there's only so much we can do.

Now, the more we learn, the more we're able to do presentations like Matt gave you and like you're going to see today, that give you some understanding of what it is we've been doing and why we're doing it. But at the—we've got some inability to give you exactly what you want. We'd love to be able to say, if it's this good, you're fine. But we—that puts boundary conditions on this industry that we're not sure is appropriate yet.

Ryan Muckenthaler:
I guess to follow that up then—and thank you very much for that information. I know that there is a—you know, we begin putting together a lot of this information. And so, if standards aren't attainable yet, would it be something that we could have a—a do-not-use list, you know, like as far as these products cannot be in your product, these raw materials?

Todd Cecil:
Again, I think that is going to be a topic to take up with the toxicologists and with the pharmacologists as we get there. There are cases where you want to use an ingredient, and we've got some of them in the HPHC list and that we are updating that HPHC list to add some additional things, but we're not adding a lot at this point in time that are ENDS specific. But it will give things like—well, I can't—I will misquote if I give you an example because I'm sure I would grab the wrong one, but there are some in there that should not be present, or you at least need to tell us that how much of that is present.

Nicotine, for instance, shows up on the HPHC list. Obviously, that needs to be present in an ENDS device if it's got nicotine in it, but it does have some potential negative consequences that need to be assessed when we look at the risks and benefits. So, we try to give as much as we can, but there—again, there's—saying do-nots—I know that Europe has done a number of saying here is the specific things you can use. Our laws are different, and we are not able to, at this point, go down that road. We will consider it, and we'll talk about it when we get back to—after today's discussion.

Ryan Muckenthaler:
Yeah, one last follow-up here.

William Wikstrom:
Go ahead.

Ryan Muckenthaler:
And only because, you know, as you said, nicotine does appear on that HPHC list. So, this is a bigger question here. But does nicotine have a place within the harm work—harm reduction framework for the American people? And, you know, I mean should Americans who do use nicotine have less harmful options than combustible cigarettes?

Todd Cecil:
I think that is a discussion to take up this afternoon. This is a product characterization, and this

is—that's not a characterization question. That is a toxicity question or a benefits question as well. And I think that both sessions will discuss the merits and—of nicotine. But that's what we're here to regulate.

Ryan Muckenthaler:
And that'll come up on which panel?

Todd Cecil:
It could be all three of them this afternoon because I'm sure that pharmacology is going to talk about nicotine. I'm sure that adult benefit will be talking about nicotine, and I know the toxicology can talk about nicotine.

Ryan Muckenthaler:
All right. Fantastic. Thank you, sir.

William Wikstrom:
Good morning, again, everyone. So, when we talk about characterization, we're talking about validated reproducible science, correct? So—and the FDA has already shown what is good enough, what it looks like when you look at the TPL review for PM0000973, the RJ Reynolds PMTA. And so, you can see everything in there. And what I'm wondering as a small business manufacturer, since you guys have already granted these marketing orders for these other products, why can't we get a substantial equivalence to something along those lines and as—and have those set out as standards for us small manufacturers?

Matthew Walters:
Just to clarify, you're talking about more method specific—sorry?

William Wikstrom:
We were talking about—you know, product characterization is the topic here. So, as I outlined, you know, we are looking for reproducible science as part of this product characterization. You know, we're talking about validation here. So, when we see that we have marketing orders granted to other companies with these products, what I want to know is that those marketing grant orders show what exactly is good enough, so based upon that predicated source, I need to understand why as a small manufacturer, since a lot of these regulations were ambiguous at the time years ago, for us small manufacturers to submit our PMTAs, why can't we get a substantial equivalence in order for us to help bridge the gap on this stuff and have the FDA look at—since you've already established what good enough is, why we can't turn that into standards so we don't have a floating-point target in order to help us be in alignment and be in compliance with submitting good PMTAs?

Matthew Walters:
Yeah. I'll start to answer, but I'm not sure if I entirely follow. But—so, correct me. I mean, if you're talking about methods specifically, you know, there are—we need to make sure that the methods are completely validated for your particular product in that laboratory. And so, there's a lot of considerations there. There are some efforts in terms of—to have standard methods that are recognized across CTP, similar to other centers. But that's a big effort.

In terms of substantial equivalence, that point, I'm not quite understanding because, you know, SE is only possible if the predicate is on the market prior to 2007 up to 2011, if you're talking about provisional. So, I don't quite understand that component of—

William Wikstrom:
Well, doesn't—but isn't it in—well, the FDA claims that everything falls under their jurisdiction through the TCA, correct? So, can we not make any adjustments to that since this is a roundtable for small manufacturers, in order for us to make—to be able to adjust on a floating-point target? For example, when you look at like, say, the RFA here, when you have the, you know, the Regulatory Flexibility Act, what you're looking at here is that there was no real pathway for small business, and hence that—why we're here today is for the FDA to talk to all of us about this stuff.

So, when you look at—and that RFA is so critical because it's supposed to be scaled—that's a federal law that's supposed to be scaled for the size of the business. But we don't have that. But we have—we now have marketing grant orders out there that shows that what is, quote, good enough in order to be granted a marketing order, which the rest of the small manufacturers do not have. So, why can't we get some kind of standard that sets some kind of substantial equivalence that's based upon, you know, the RFA in order for us to be successful? Because it's not like we're trying to come up with something here and just submit anything and see what sticks. Everybody here is trying to get a marketing grant order too, myself included. So, I'm looking at, if this is what's good enough, then why can't they—what is preventing the FDA from—who is in charge of this stuff—scaling this to what adjusts and fits for small businesses since we've already seen these grant orders show what is good enough?

Todd Cecil:
Bill, can I step in and say, I think that what you're asking is not part of product characterization. What you're talking about is APPH or changing the standard with which we determine whether or not a product should be on the marketplace. What you're suggesting is that we change the law to—and allow substantial equivalence approaches for small business. Now, that is not something that we can do without going through a rules process. And sure, there's the potential we could do that. It will be years in the making. But I cannot and will not promise that we will take that up necessarily. We will discuss it.

William Wikstrom:
Yeah.

Todd Cecil:
We absolutely will talk about it. But I don't think that it's something that has to do with product characterization.

William Wikstrom:
Well, this comes directly off of your guys' stuff on product characterization. So, that's why I'm bringing it here. And it comes directly from the way you guys have product characterization. So, that's why I bring it up.

Todd Cecil:
Well, okay, you can point me to where you want—or where that is, but I think that when we talk about validation, we're talking about—every one of us is going to talk about validation differently because we—every measurement must be valid. If we're going to talk about substantial equivalence, we're going to say that the—that your product is not significantly different than a product that has been authorized. Now, the only way you can show that is if you have inside information into the design of that product, and you have an understanding of what all of the ingredients are that are in that product and all of the plastics that are used in the manufacture of that other manufacturer's product so that we can understand what is different. But that is not allowed for a new product on the marketplace. That is only for revisions to existing products. And that is what this SE in the TCA talks about.

William Wikstrom:
Yeah, and I understand that. I get that because I already have an existing product. I was looking more along the lines of, like, the propylene glycol, the vegetable glycerin, and the nicotine and stuff like that. So—and at the end of the day, I'm just looking at it as trying to help—I'm telling you, this is my concern. I'm looking at it from a small business point of view, because without any investments and a pathway for success, you know, how is an American manufacturer supposed to thrive, especially when our nation has been inundated the past few years with products flooding in from outside the United States that are literally putting American manufacturers out of business because they are completely ignoring your authority?

And so, I'm trying to find a way to see where we can bridge that gap and find something that works for small business based upon the regulatory framework that we have to work with. And so, when we have that Flexibility Act, you know, just scaling it down and finding stuff that can be a standard for all of us to use, from the product design to the—you know, that's part of the characterization, you know, and the reproducible science. And that's why I'm talking about the—you know, the PG, the VG, and stuff like that. And at least just give us some standards. Give us a solid target to shoot at. That's exactly what I'm asking.

Todd Cecil:
Okay. I appreciate your redirection saying let's talk about PG/VG nicotine when you're buying that material. I think that's something that is within the boundary conditions of product characterization. And I don't know if we—there are standards that exist out there, and I can turn to Colleen or Matt to talk about the standards that they're comfortable with. But again, we—these are by no means required.

Matthew Walters:
Yeah, I just comment. I mean, for nicotine PG/VG, you know, we obviously want to make sure it's of high grade, limited impurities. I'm sure that's probably what you guys want too, when you choose your ingredients for your product. And so, that's obviously a consideration that we make in not only for product characterization, but toxicology a way or not to make sure that there's no increase in impurities. And we want to make sure that your ingredient choice is of the highest possible quality that you can find and you'll use, so.

Todd Cecil:
And an example is for propylene glycol and glycerin. Both of them have and historically been adulterated with diethylene glycol that has killed hundreds of people over the years. It's something that a manufacturer or a small business should be watching for and ensuring that there is no diethylene glycol, no ethylene glycol present. And there are—again, there's lots of standards in the pharmaceutical industry that deal with PG and VG. And, you know, we can direct you towards those. We can't require it of you, but it may be something you want to look at.

William Wikstrom:
Thank you.

Todd Cecil:
Sure.

William Tang:
I have another question. Yeah. I have read a paper from CTP published in 2024. In the paper, it describes that 36 HPHCs or 93 HPCs can be qualified [unintelligible]. So, I want to know next steps—CTP has another plan to release some standard or guidance for the 36 HPHCs so that gives some specific values about the 36 HPHCs so that for us, for the small manufacturer, we can use this as our standard to judge and control the product qualities, yeah.

Matthew Walters:
So, just to clarify, you were asking about, you know, certain HPHCs are not detected and—but you're still expected to report on those, is that—maybe I missed—maybe, Todd, you understood that.

Todd Cecil:
I'm not sure which paper it was in 2024 that you're referring to. I was hoping that—but I know that the HPHC list is—we are working to update the HPHC list, and hopefully, we'll have that done sometime soon, and we'll be able to present that. And that will have an extension of HPHCs. But I don't think that deals with the methods themselves. Am I right to understand that there was a paper that you were referring to that measured 36 HPHCs?

William Tang:
Yes. I want to know next step. CTP will release some guidance for the specific values about the 36 HPHCs, yeah.

Matthew Walters:
And these HPHCs are just for ENDS? Is that the paper about?

William Tang:
Yeah. Yes.

Matthew Walters:
Okay. Yeah, I think, you know there are efforts and considerations about how we articulate what HPHCs are in different matrix. And so, we're working through what that may look like for—and

the next step could be a guidance or some effort, but we're working through the science there to figure out what HPHCs should be reported on. There's a—you know, 93, 100 and something HPHCs which I know they're not all in ENDS products. So, we're working through some of those efforts there.

William Tang:
Okay. Thanks.

Todd Cecil:
Mark.

Mark Anton:
I'm going to touch on probably the third rail in this subject because it is product characterization. And myself and many of the small businesses up here have made their living, created their businesses with the introduction of flavors. And as we see currently, we have to compare the efficacy of a flavor to show substantially or some level of benefit above a tobacco flavor. As individuals—as someone been in this business, I've seen, collectively, flavors have a massive impact. Individually, it's part of a process that the consumer goes through. So, they might not show that particular statistic that the FDA is looking for.

So, how is a small businessperson who's putting forth 200 flavors, right, so, that's going to water down their viability. But collectively, they might show a 200-percent increase of staying smoke-free or reduced smoking or whatever the standard is. So, I think that, here, we have an issue where open systems, which I'm in, is a much harder segment to get an approval. And flavors, we all know the conversation that's gone around that. And that's not what I'm here for.

But I'm here to look really at the point of how does a flavor get even to the table, right? Because we see, as we—they talked about the flood of the Chinese. It's 88 percent of the marketplace, and there—it's all flavors, right? So, we see the consumers need it. So, how do we, FDA and us manufacturers, work together to bridge this gap to get to a place where we have, maybe, some common ground, if you will?

Todd Cecil:
I will split your question. First of all, the suite of flavors that you're talking about and the comparison versus tobacco flavors are things that need to be taken up in adult benefit. And that's this afternoon. All right. And I think that is—as we talk about the relative benefits that are provided by the flavors—

Mark Anton:
That is a product.

Todd Cecil:
—let me—no, it's not. Product characterization is, when you give me your list of flavors, do you give me all of the ingredients? The questions that I wanted to throw out there is, you know, what challenges do you face? To a certain degree, we can address some of them, but we would like to hear that sort of information discussion, because if we do not have all of the ingredients, we're

not going to even look at your application. We can't. We need to have all that information. So, what—and let me just throw that out there and see what you guys can provide.

Ryan Muckenthaler:
I mean, from an e-liquid manufacturing standpoint, yes, the complex flavor ingredients was a difficult aspect of the PMTAs. We did have some flavor manufacturers that were unwilling to submit their recipes to you on a tobacco product master file. I guess the only help with that would be, I guess, the list of manufacturers you want me to use flavors of.

I'm sorry to keep harping on this, you know, but yeah, I mean, if I had a go-to, I would absolutely use that. It's like what you talked about with the PG, the VG being USP grade, you know. I mean, that is a standard set, and we, you know, do not deviate from that. And it would make my process, the application process, our business decisions much easier if we knew what flavor manufacturers to, you know—who achieves that standard, that high bar, and we would use only them.

Todd Cecil:
Do you have a problem getting a manufacturer to be forthright with you on what those ingredients are or at least to develop it in TPMF? Do you then say, well, I can't work with you? Do you have any leverage with these manufacturers?

Ryan Muckenthaler:
There was a number of them that were willing to work with us work with you. You know, they see great value, not only in the business aspect of it, but, you know, they are passionate about the vapor marketplace as well. And so, they're invested in it. We did run into a few, though, I think, not to name names, but there was one specific that absolutely would not do anything with it. So, most were willing to at least attempt, with a few being successful, I think, with creating a robust TPMF. So, is that—

Matthew Walters:
Sorry, I was just going to ask, similarly, what was the rationale why they didn't want to provide that information, but you sort of answered that. That just is quite a challenge if they're not willing to work in how to get that information to FDA because it is proprietary. So, yeah, yeah, I don't have a solution [unintelligible].

[laughter]

Ryan Muckenthaler:
Right now, we won't be able to—I mean, obviously, we couldn't use them anymore. So, those flavors are gone. So, that was our only solution. But that's, you know—we weren't able to submit a PMTA for it, so that's what we had to make.

Geoff Habicht:
I just want to add something to this too, because I think product characterization on both the hardware side and the liquid side presents a unique challenge for, the whole process creates a unique challenge for those of us that are in one space or the other, yeah? And it's a bit of a catch-

22 for us as well, because as a small manufacturer, we—without a set of objective and measurable outcomes that we're working towards, we cannot invest, we cannot raise money, we cannot access the capital markets, right? It's an important business piece that I think the FDA needs to understand about small business.

When we're not sitting on $6 billion in cash that we can then go and test for everything, we have to be very smart and strategic about how we come to market. And I would think that it's the FDA's goal, and should be, to work in partnership with us to get us approved and through. Because since we've been in this market since 2008, when we, the small businesses, were the innovators in this space, we've gone from 45 million smokers in the U.S. to 25 million smokers in the U.S. A large portion of that is attributable to us getting people to switch to less harmful products, anecdotally, less harmful, because we haven't gotten the FDA to say these are appropriate for the protection of public health.

So, you understand the—we're in this position where we don't know where and how to move forward unless we have a set of objective standards. You can call them standards or benchmarks. It can be as simple as we know that if the temperature on a coil gets above X, it's going to cause combustion. Your coil temperatures can't go above X, right? And that's calculus. It's thermodynamics and the type of materials and time for shut off and the power and the water—like, you know this. It's—we can do the math. And you can validate that through testing.

The e-liquid guys need me, as a hardware manufacturer, to have that set of standards because then they can say, well, I can pick a product that meets all of these things, and then I can test my e-liquids, right? I need the e-liquids to have a set of those things. Because whether it's a do not use list, a do not exceed list, a generally recognized as safe for aerosols, which we don't necessarily have today, but there's a lot of data out there in a lot of TP master files that you have access to, right, that could publish potentially a list of those things without giving out the data.

But it would allow us then, as hardware manufacturers, to be able to go and say, okay, we're going to test our products with these ingredients or these e-liquids that we know kind of fit that set of benchmarks. So, it's an important piece of the characterization because those are the details that we need in order to then get into doing PK—you know, whether it's a study or, you know, a simulation or whatever the case may be.

Todd Cecil:
Karen, you want to talk about design or—

Karen Coyne:
[unintelligible]

Todd Cecil:
You don't have to. I have a response, but I—one of the things I want to point out is TPMFs, we don't have access to them, generally. They have to be referenced, and I can only look at them relative to what you have. It is double blinded. We're not allowed to look at them unless we have authorization to look at them. And everybody who opens it has to sign that they've looked at it. So, you know, we cannot go in and just say, here's all of the TPMFs and all the stuff that we've

got. We don't have access.

So, when you have an LOA that allows you to—letter of authorization that allows you to say, I can look at the TPMF, then we can look at that and consider what's in it. And we have to consider it relative to a single application rather than all of them. And so, we are restricted on what we can do that way. But I certainly understand where you're coming from. I know that it is something that we are working on. We are in the beginning stages of it. And I think there is an opportunity for us to reach out more and ask for some more information when we are in a position where we can.

But I think there is a lot of great information that we can take away from small manufacturers or device-specific manufacturers, open e-liquid manufacturers. So, we will be reaching out and at least considering it as we are able to. Bill.

William Wikstrom:
I have another question. So, when we're—and this kind of fits in under what he was talking about in flavors, but not sure if it falls under product characterization or not. But when you have an e-liquid manufacturer that has multiple different flavors, under product characterization at least, when—do we really have to treat every flavor as its own novel product when they are all almost exactly the same as far as, chemically, on, you know, three of these, such as 3 milligram, the PG/VG ratio, and the only different thing in it is the flavor? Would that—you know, do we have to treat every flavor as a novel product in and of itself just because there was a change in the flavor? Can we not just make this one standard thing for us to work with, chemically, where the only thing that has changed is just the flavor?

Matthew Walter:
Yeah. So, this is more of a review issue, but we do have our approach to consider what we call internally, a bundling and bracketing approach. We will bundle similar flavors, for example, a fruity flavor, they could be bundled together, and similarly with different or similar concentrations of nicotine, PG/VG. So, we do consider sort of the worst-case type scenarios in grouping flavors together as appropriate and what makes sense, yeah.

William Wikstrom:
And that's—I guess what I was alluding to, instead of having, you know, the burden of filing so many documents for each different flavor, if we could just submit them under one standard PMTA and then just annotate that this flavor is now here or kind of break it down so you don't have to file so many documents for just, you know, for just one flavor and treating it like a novel thing.

So, if you have, okay, this is this particular range of, say, fruity and can we just get it to where we have a PMTA that has standardized PG/VG, nicotine, the different labels, the container or product packaging in it, and then just breakouts within that PMTA that say, okay, this particular one has this flavor. This flavor name has this particular flavor in it. So, that's what I'm looking for, to try and streamline the process, something that's more efficient.

Matthew Walters:

Yeah. I have to say, we try to have some more efficiencies on the scientific review part, as I just mentioned. That being said, we do have to issue, you know, actions on one STN based on the characteristics of that—each product. But we may take some approaches during the scientific review part of it.

Todd Cecil:
And keep in mind, there have been a number of papers out there that have demonstrated that different flavors actually change the nicotine release. And so, if we just say, well, every flavor is just another flavor, that's not the case. Plus, different flavors have potentially genotoxic ingredients in them, not all of them do, but some of them do. And we have to understand what those are and think about what that does to the overall risk of use of that product, whether it is appropriate for the protection of public health, right? So, that's one of the reasons.

Now, the other is that every applic—every individual flavor is a different product. You call it something different. You name it something different. You package it differently. It is a different product from the legal regulatory perspective. So, there needs to be a separate application for it. However, you can reference information that is consistent across them. The PK, for instance, our pharmacologists will talk about that, can be considered the same. The—obviously, they're going to have to show nicotine release or the amount of nicotine in the aerosol, right, for every one of those flavors, because it might change. We don't know which flavors cause that. Every publication I've seen has a different set of flavors that cause nicotine to increase by up to 200 percent. So, it's something we have to understand. We need to see the testing to demonstrate, right?

So, we can't just say all of these fruit flavors are okay. We need to know that each one of them is okay. So, we do require consistent and—testing of each product, but there are places where we don't need to, where you can bridge across flavors. And I think pharmacokinetics is one of those, and I think that they'll talk about that. But again, that assumes the nicotine release is consistent. And so, I think there's a—all of the pieces fit together. No single part of this lives on its own. And so, you know, product characterization is a critical piece. If we don't know the characterization, we can't predict some of the other things that come along.

Willam Wikstrom:
Yeah. I was never trying to characterize it as anything other than that. I'm just trying to find something that is more streamlined and more efficient and less paperwork because it's—all the regulations and all of the paperwork, it's literally strangling the small businesses. And so, I'm just looking for ways to work with the FDA to make sure that we can meet those goals of being granted a marketing order and looking at these things in order—because it's not just product characterization. We have four other panels to go through today. And as you said, this is one piece of that pie. And so, I'm reaching out to you saying, hey, is there a way we can at least streamline the product characterization? That's really what I'm digging at here.

Todd Cecil:
There should be a number of places where you can bridge across, so.

William Wikstrom:

Thank you.

Geoff Habicht:
I have a different product characterization question, which is this industry is one that moves very quickly. Innovation happens very fast. And, you know, you move from wrapped coils to ceramic or even laser cut, right, which changes the way in which it—you know, the metal actually—you talked about—not leachables, but I'm blanking, but you know what I mean? Right. So, we can minimize those things by changing some of the ways in which we actually construct these from an engineering perspective. Another catch-22 that we end up in is if I have a PMTA, let's say, hypothetically, but not hypothetically, that was submitted in September of 2020 and accepted for review in 2021, and now, we're five years later, and I haven't heard a single thing. And I want—I have updates that I need to make to that. Whereas the only way for me to make those updates is to submit a new PMTA and go through this process all over again, which puts me then at the back of the line, which we don't know if the line has ever moved because we don't hear anything. There isn't back and forth. And as I said earlier, we will—we want to comply. We want to work with the FDA. And communication is a lot less expensive than litigation.

Todd Cecil:
No question about that. We much prefer that. Let me also offer that amendments to an application are not abnormal. In fact, they're encouraged. Anything that comes in prior to us sending you a letter saying we're kicking off your review will be considered. So, feel free to make the changes you need to make.

Geoff Habicht:
But the review—we're kicking off the review came in 2020, late 2021, 2022.

Todd Cecil:
That—well, there, I'm not sure. I—obviously, we can't talk about that one. But if there is a—if you've received a filing letter, that doesn't mean that the review has begun.

Geoff Habicht:
I know.

Todd Cecil:
Okay.

Geoff Habicht:
Yeah.

Todd Cecil:
Got it, yes.

Geoff Habicht:
So who do I follow up with on that, is the question.

Todd Cecil:

Right, yeah. And anything that comes in after the fact will be considered. It'll be a new major amendment, and it depends upon what that change is. If you are now changing a fundamental piece of it, we're going to have to start all over again. But again, amendments that come in will be considered.

William Wikstrom:
I would like to point out, I had no idea we could ever submit any amendments in any way, shape, or form. And finding that out now, 5 years later, I mean that makes a huge world of a difference because I'd have been—I would have focused on making sure that I was meeting these target goals that you guys are looking for instead of finding that out right now. And I really would like to be able, when this panel is over, to discuss this with somebody after the day is rounded up or after this panel is over, because that makes such a huge world of difference. Had I known that, I would have continued to work on these PMTAs in order to give you what you guys are looking for. Because again, all of us small manufacturers are looking for that marketing—you know, being granted that marketing order as—just as the other companies that have already been granted marketing orders. That's all.

Todd Cecil:
No, that's fair. And I would reach out to your RHPM. Each of you should have received the name of an RHPM when you got your filing letter. Yeah. That has been something we've—no, that's fine, yeah. My RHPM is correcting me. We can't take an amendment to add a new product.

William Wikstrom:
[unintelligible]

Todd Cecil:
Fine. You can amend with data and so forth, so yes. Thank you. That's why they keep me in line. I love that. But yes, I mean—but if you reach out to the RHPM, if you do not—aren't able to find the RHPM, you can reach out to Cristi Stark. She is—yes.

William Wikstrom:
[unintelligible], I don't want to interfere with [unintelligible].

Todd Cecil:
She's not here. She's home with the flu. Otherwise I'd be pointing at her. But at least she can get you to the right person or pass you along, so.

William Wikstrom:
That's her, isn't it?

[laughter]

I'll go talk to you after [unintelligible].

Ryan Muckenthaler:
Before we move on to the next topic, can we hop backwards? Just one real point of clarification

here, I think that Matt had said something about it, and, Todd, I think you kind of referenced it as well. But is the FDA open to accepting, I guess, us using literature to compare for HPHC data?

Matthew Walters:
Yeah, I think it's possible. I mean, we—if it's, you know, a peer-reviewed publication, that is one avenue to provide HPHCs of, you know, marketed ENDS products. We obviously want the HPHCs measured in the new product. That's very important. But there are other avenues than testing, whether go through a process of testing cigarettes and ENDS, because a lot of those things—there are a lot of literature on those HPHCs at this point in time. But measurement of HPHCs on the new product is vital, so yeah.

Ryan Muckenthaler:
Of course. So, we can use some literature to reduce some of the testing burden then and possibly some bridging as well there.

Matthew Walters:
Yeah, it's possible. Obviously, rationale in your PMTA explaining what your approach was—

Ryan Muckenthaler:
Okay.

Matthew Walters:
—help us understand, that's obviously very vital as well.

Ryan Muckenthaler:
All right. I'm just going to need that list of peer-reviewed HPHC studies.

[crosstalk]

Karen Coyne:
Mark --

Mark Anton:
Yes.

Karen Coyne:
Before you go, can I jump back?

Mark Anton:
Go right ahead.

Karen Coyne:
Adding a coil, as DRPM pointed out, it's a new—it would get its own STN, but you can submit for that coil and link back to the other PMTA. So, you can link back to the device that you submitted previously and use—it just becomes another STN, another part of your device product. Did I say that correctly?

Male Speaker:
Components and parts.

Karen Coyne:
The coil gets a new STN. You can submit a new STN. It's a new submission? No? It can't be an amendment? But the studies that they submitted for their other PMTA and testing can be linked? No?

Todd Cecil:
I'd work with the RHPM.

Karen Coyne:
Okay. RHPM.

Mark Anton:
If I can, I'd like to direct this question towards Matt. In design specifications, it talks about the upper and lower range in a device, like—so, some of these folks make liquids, and then they're arbitrarily going to be picking a product to utilize with their testing house that may or may not get a PMTA authorization.

My question is why are you picking a high and a low range, which is really kind of an arbitrary assessment when you think about the variability of devices out there? Why wouldn't it be something structured more along the lines of the boil point or the flash point of the liquid that you're trying to deliver, right?

And then do ranges above and beyond to, you know—because we know, as Geoff said, you know, the more temperature we add, the more potential there is for HPHCs creation and, conversely, lower. It really is something that should be looked at as, you know, from the baseline of a liquid, what is the potential of this device to go beyond?

Like, I've looked at this industry, and I've said I don't know how you make a liquid and maintain a brand without having the mechanism to deliver it consistently, right? In the open-source system, that's where we are. But really, that's where the manufacturer would look at it from the standpoint of boil point and then parameters above and below, that I think would give a more statistically reliable mathematical model that we could actually say, yeah, it is appropriate.

Matthew Walters:
So, for the device part I will turn to Karen for that part, but—I don't know if she has anything to add. But I think the point about the boiling point, something we can definitely consider. Open e-liquids is challenging for everyone. I don't have great recommendations for that at this point, but I know it's a very challenging market, and the approach that makes sense for all. But I'm not sure if I'm answering the question, but I think we can consider that in the approach. But I'll turn to Karen if she has any engineering aspects.

Karen Coyne:

I would appreciate it if you would repeat the engineering aspect. I was trying to get an answer for the coil. Sorry.

Mark Anton:
I was—I'm questioning why the rationale for doing a higher and a lower range limit in the HPHCs when you're picking out devices that are arbitrary, at best, right? And one device could be 100-watt device, and another one could be 25, right? So, you're going to get varying points. It really should be off of the liquid which has a boil point attributed to its construction. And so, you know, from there you can do ranges and find out where you're going to get the higher limits of HPHCs, right? Because a customer may not even use the device that it was tested in, right? So.

Karen Coyne:
So, for an open e-liquid, if you're testing with different devices, you can do the bridging just like you could with the e-liquid. So, you could test at a lower-power device or a lower power—a lower temperature device as well as a higher power device or a higher temperature to show the impact of the temperature or the power on the e-liquid—the HPHCs.

Todd Cecil:
And we do appreciate your, you know, recommendation. I think it's a good point to raise, and I think we will take it back and consider it. We are up at the end of this session. I want to thank all of you. I want to thank my FDA colleagues. I'd like to thank the small business that came here and represented yourselves and asked great questions and gave us great information. With that, we're going to take a 10-minute break. We'll be back here at, well, all right, 35 after, maybe 37 after.

Male Speaker:
Thank you.

Todd Cecil:
Thank you.

Male Speaker:
Thank you very much.

[break]

[music playing]

Todd Cecil:
Welcome back, everyone. Thank you very much for coming back and joining us for this next session. The next session will take us up to lunchtime, and while most of you were in attendance for the last session, we have the folks online who may not have heard what was going on in the first half. So, I'm going to cover some of the same ground. So, you can ignore this first part if you've been here before.

So, this session will begin with a brief presentation on the information that FDA uses for

evaluation of APPH and ENDS products. These presentations are not intended to cover everything that is considered, how decisions are made, but instead are intended to present a brief primer on the topic so we all know what a topic entails and what types of information that we intend to discuss. These are scientific topics that deal with what FDA considers during a review process. We will be—not be discussing logistics of a submission, the timing of a submission, the specifics of any application.

These presentations are intended to be brief, about 20 minutes in length. After the presentation, I will introduce the participants in the roundtable, or they'll introduce themselves. Each participant will be given no more than 2 minutes to introduce themselves, where they work, whom they represent, and as appropriate, a brief explanation of their experience. Discussion will be limited to individuals in the roundtable and may involve moderator offering questions on certain topics to spark discussion. These topics may be taken from the questions submitted in the docket but are not limited to this source.

A moderator will be expected to intercede in the discussion goes off topic. Again, I'm talking to myself in third person, but—and to move the discussion along if we are covering ground already discussed. However, at the end of the day, our goal is to answer those questions that we can and to listen to stakeholders on the panel to understand the difficulties that small businesses must overcome and, hopefully, ideas on ways to reduce those difficulties.

So, this second session pertains to the topic of manufacturing control. Manufacturing control relates to a number of foundational pieces of information that we rely upon to define what a product is, how a product is made, how a manufacturer ensures that a users obtain a consistent product, and how variable is that product. These questions define, support, and inform discussions and considerations of the toxicological profile, the pharmacological profile, and to some degree, the epidemiological profile. We'll be talking about each of these in due course.

So, we'll begin this discussion with a presentation of what our reviewers are looking for with respect to manufacturing control information. So, our first presenter for this session or our presenter for this session is Dr. Karen Coyne. Karen is an engineer and has been with the Center for Tobacco Products, the Office of Science, for 10 years. She started her tenure with us in 2016 and has been involved as an engineering reviewer, a team supervisor, and is now an Associate Director of the Division of Product Science. Dr. Cohen has extensive experience in review of PMTA applications and the needs of manufacturing controls of these—in these reviews. So, with that, let me turn the floor over to Karen, and she will—

Karen Coyne:
Good morning, everyone. Thank you, Dr. Cecil, for that introduction.

Earlier today, Commander Walters discussed the importance of product characterization for ENDS products. But how do you know that the product you've designed is the product that gets into your consumer's hands? You do this through a well-controlled manufacturing process. So, today, we'll cover the essential elements of manufacturing documentation, quality management systems, and risk mitigation strategies that are fundamental to successful PMTA submission. These requirements aren't just regulatory checkboxes. They're critical to ensuring product

consistency and demonstrating that the products are appropriate for the protection of public health.

Let me start by providing some context for why manufacturing information is so crucial to the PMTA review process. The manufacturing process encompasses everything from supplier qualifications and raw material receipt through finished product distribution. A well-documented manufacturing process demonstrates that you can consistently produce products that match what is tested in your scientific studies. This consistency is essential because your product, the products consumer use, must be the same as those evaluated in your toxicological, behavioral, and abuse liability studies.

If you don't have proper cleaning procedures, you can introduce microbial contamination into your e-liquid that the consumer may inhale. If the gasket on the pods is slightly undersized, you can have leakage and the potential for accidental exposure. If the nicotine content in the e-liquid is higher than specified, abuse liability may be impacted. If the device doesn't shut off when the temperature reaches the stated cutoff, there may be overheating, fire, or explosion. Without assurance of manufacturing consistency, we cannot accurately assess the public health impact of your product.

The foundation of consistent manufacturing is a robust quality management system, or QMS. Your QMS can be based on recognized standards such as ISO 9001, which provides a comprehensive framework for quality management. A complete QMS must establish and document comprehensive quality procedures across several key areas. These include incoming inspection of raw materials, in-process controls during manufacturing, finished product testing, procedures for handling non-conforming products, corrective action protocols, and document control systems.

It's important to understand that your QMS should address both quality assurance and quality control. Quality assurance is process oriented and focuses on preventing defects before they occur. This might include training programs, equipment maintenance schedules, and process validation. Quality control, on the other hand, is product oriented and focuses on detecting defects through testing and inspection. Both aspects are essential for ensuring product consistency and safety.

Now let's discuss the specific documentation that forms the backbone of your manufacturing process. There are four critical types of documents you need to provide in your PMTA, which are a subset of the documentation outlined in the PMTA rule in 21 CFR 1114.7(j)(2). First, standard operating procedures, or SOPs. These should cover all critical manufacturing steps and clearly specify who performs each operation, what is being done, and when it occurs. SOPs provide the high-level framework for your operations.

Second, work instructions, or WIs. These provide detailed, step-by-step instructions on how to complete specific tasks. They may be an independent document or part of an SOP.

Third, Certificates of Analysis or COAs. These documents demonstrate that you're consistently manufacturing within your established specifications or that your purchase components meet

your specifications. They provide objective evidence of product quality.

Finally, batch records. These are complete production and control documentation for each manufacturing batch, capturing who did what, when they did it, and how they did it. Batch records are evidence that you followed your standardized procedures for every single batch produced, ensuring that the product consistently meets quality and safety standards.

Now let me highlight four key considerations that are central to demonstrating product consistency and manufacturing control. First, you must demonstrate product consistency through your SOPs, work instructions, COAs, and batch records. These documents should tell a coherent story about how you maintain consistency batch after batch. Second, your manufacturing specifications must align with your labels or labeling for nicotine. If your label or labeling says a product contains 5 percent nicotine, your manufacturing specifications and actual production data must support this.

Third, you need to provide information to demonstrate that your products are both chemically and microbiologically stable throughout their shelf life. Products that degrade or become contaminated pose risks to customers. Fourth, you must provide information supporting the intended function of all features designed to mitigate risks associated with your products. If you state that a safety feature works a certain way, you need to provide evidence to support this.

Let me now share some of the most common issues we have encountered. We often see incomplete manufacturing process descriptions and procedures. Some applications lack critical SOPs or work instructions, for example, procedures for handling non-conforming products or training new employees. Many applications also fail to include examples of the relevant forms and records they reference.

Inadequate quality control is another frequent problem. This includes missing functional testing of product features or insufficient performance verification data. We also commonly see incomplete information about manufacturing steps. For instance, the source of components may be unclear, information about how you accept or reject incoming materials may be missing, or assembly steps may not be fully described. Reviewers need to understand your entire process to assess whether you can consistently manufacture a product to your design.

Beyond process descriptions, we also see some recurring issues with QMS documents themselves. SOPs frequently lack sufficient detail or contain unclear instructions. If your employees would struggle to follow an SOP, it doesn't contain sufficient information for regulatory review.

Work instructions often fail to include acceptance criteria for in-process checks. It's not enough to say you check something. You need to specify what constitutes an acceptable result. COAs are frequently incomplete. They may be missing target specifications with units, quantitative acceptance criteria with units, test data averages, or statistical measures like standard deviation or minimum and maximum values. Finally, batch records often contain incomplete information such as missing manufacturing steps or in-process test results with their associated acceptance or pass-fail criteria. Every step in every check should be documented.

Let's talk specifically about nicotine specifications, which are critically important for tobacco products. You must provide target nicotine quantity specifications along with upper and lower range limits and acceptance criteria for your finished products. These specifications define what constitutes an acceptable product. You should also include in-process checks to ensure nicotine quantity remains within specifications at each manufacturing step.

Finally, you must demonstrate that your target specifications and acceptance criteria are actually met using your manufacturing information, such as batch release data. Show us the data that proves your process works as intended.

Why do we emphasize nicotine control so strongly? It's because the consequences of poor nicotine control are significant for public health. If nicotine quantity is not well controlled, consumers will not receive a consistent product. This inconsistency may lead them to use the product more frequently to achieve their desired effect, potentially increasing their overall exposure. When consumer use patterns vary due to inconsistent nicotine delivery, exposure to harmful and potentially harmful constituents, or HPHCs, may be higher than you anticipated in your toxicological assessments.

Abuse liability may also be impacted. A product with higher than intended nicotine quantities may be more addictive than your studies indicate. Perhaps most fundamentally, if nicotine levels vary, we won't know whether the products used in your abuse liability and other clinical studies are truly representative of what consumers will experience in the real world. This undermines the scientific foundation of your application.

Now let's discuss stability studies which are essential for demonstrating product integrity over time. Stability studies demonstrate that your product remains stable throughout its shelf life and that key product characteristics such as nicotine quantity, water activity, and pH remain within acceptable ranges over time. This matters because products may undergo chemical or microbial changes that create new HPHCs or increase existing ones. These changes could significantly impact public health. Stability studies ensure that consumers use a stable product throughout its shelf life and aren't exposed to degradation products or microbial contamination.

Let's discuss some key factors for adequate stability studies. First, ensure your stability studies reflect your claimed product shelf life. If you claim a 2-year shelf life, your study should cover that full period. Stability studies must use at least three time points: the beginning, middle, and end of the shelf life. This allows you to track changes over time and identify any trends.

Something important I want to highlight is that if your stability study doesn't support the shelf life you've specified, your product may receive a marketing granted order only for the shelf life that your stability study actually supports. Conduct testing at your intended controlled storage conditions, including the temperature and relative humidity. If the products will be stored at room temperature, test them at room temperature. Finally, accelerated studies are not appropriate for microbial stability studies because microbes require specific environmental conditions to survive. Only real-time studies can accurately predict their viability. Real-time studies are necessary for microbial stability.

A few additional points about stability studies. If your testing is conducted by a third-party laboratory that uses a tobacco product master file, or TPMF, you must ensure that a letter of authorization to use that TMF is included in your application. Without that authorization, we cannot reference the data in the TPMF.

Your stability studies must use validated methods. You should provide both the validation data and the test methods themselves. Data from unvalidated test methods simply don't provide confidence that the results are accurate, repeatable, and representative of your finished product. Validation is not optional. It's essential for scientific credibility.

Moving to risk analysis, FDA recommends you conduct a failure mode and effects analysis, or FMEA, or another systematic risk analysis approach. The purpose is to identify design and process risks, and the mitigations you've implemented to address them. It should also verify that no additional risks were introduced during the manufacturing stages.

If new risks were identified during manufacturing, you must include evidence of how you've mitigated them, for example, in a process FMEA. Why does this matter? Because mitigation of design and process risks is directly associated with protection of public health. Products with unmitigated risks pose greater dangers to consumers and may not be appropriate for the protection of public health.

Let me provide you with some examples of common features that mitigate risk, particularly for ENDS. Maximum puff duration limits can prevent overheating and excessive exposure to nicotine and other HPHCs. Timeout functions provide automatic shutoff after a specified use period, preventing continuous use that could lead to overheating or excessive exposure. Temperature controls mitigate excessive heating, which could increase HPHCs or cause burns. Low-voltage cutoff protects the battery from over discharge, which could lead to battery failure or safety issues.

Each of these features serves a specific public health protection function and if included, we recommend you demonstrate they work as intended and can be manufactured consistently. How do you demonstrate that your risk mitigation features work? You do this through comprehensive testing. First, consider how features affects constituents emitted from your products. For example, does your maximum puff duration limit actually reduce HPHC emissions compared to unlimited puff duration?

Confirm that features operate as intended under normal conditions, but don't stop there. You must also test your products under abnormal and misuse conditions. Products don't always get used exactly as intended, and you need to understand what happens when they don't. Explain how features are tested and measured and indicate whether your tests comply with industry standards such as ISO or UL standards. These established standards provide credibility to your testing approach. Finally, report adverse experiences and explain how they are documented and resolved. If consumer problems occur, you need systems in place to capture, investigate, and address them.

Let's focus specifically now on batteries and devices where we see particular challenges. Common missing information includes the normal operating region for the battery, descriptions and testing of protective circuits and controls, power system parameters, and battery and device test methods and data. Several approaches may be taken to address these issues and properly mitigate risks.

Test the whole system, the battery, the device with the battery, the power supply, and the protective circuits and controls. The interaction between components is critical to understanding real world performance and safety. Consider incorporating electronics industry standards for batteries and devices. These standards, such as UL or IEC standards, have been developed specifically to address battery and device safety. Integrated, device-specific, or inaccessible cells and batteries may also mitigate risk.

Device construction and materials should be tested to ensure the device will withstand anticipated physical abuse, for example, crash-and-drop tests to reduce overheat, fire, and explosion. Devices should be tested with the cell or battery. Finally, power supplies, which may be universal or device specific that are tested to industry standards may mitigate risks.

Let me conclude with four key takeaways from today's presentation. First, provide complete manufacturing process information, including SOPs and work instructions, to cover all processing steps from sample receipt through shipping of finished products. Completeness is essential. Second, demonstrate that nicotine quantity in your finished product meets your specifications. This is fundamental to product consistency and assessing whether the products are appropriate for the protection of public health. Third, conduct sufficient chemical and microbial stability studies to demonstrate product integrity over your claimed shelf life. Finally, provide information to support the intended function of all features that mitigate risks associated with your new product.

Thank you for your attention. These manufacturing requirements may seem extensive, but they're essential for ensuring that the products reaching consumers are consistent and appropriate for the protection of public health.

Todd Cecil:
Thank you, Karen. I appreciate it. We're going to do introductions again, as in last time, and we're going to ask Colleen and Matt and Karen to introduce themselves again. There are different—potentially different people online, and we want to make sure that we are not anonymous over here. So, let me go ahead and turn to Colleen Rogers first.

Colleen Rogers:
Good morning. I'm Dr. Colleen Rogers, the Director of the Division of Product Science. And our DPS staff are the ones that look at product characterization and the product manufacturing parts of the applications.

Matthew Walters:
Good morning. I'm Commander Matt Walters. I'm the Deputy Division Director in the Division of Product Science and I have chief responsibility overseeing the chemistry discipline.

Karen Coyne:
Good morning. I'm Dr. Karen Coyne. I'm the Associate Division Director at the Division of Product Science, and I am an engineer.

Todd Cecil:
Bryan.

Bryan Burd:
Good morning, everyone. I'm Bryan Burd with Chemular. We are a regulatory consulting company. I've been working on PMTAs for close to 11 years now, providing regulatory advice. I'm here on behalf of NEPA Wholesale, their scientific advisor. NEPA is a great example of a small business in America. They're quick to adapt. They're—provide a lot of innovation, employ a lot of people locally, and appreciate this opportunity to discuss with the FDA. Thank you.

Charles Melander:
Hi, I'm Chuck Melander. I'm here on behalf of Streamline Vape Company where I serve as the Chief Strategy Officer. Streamline is one of the early innovators in the ENDS space and has been an active participant in the PMTA process since the beginning. Began my career with Swedish Tobacco Company, which is now Swedish Match, back in 1982, where I started the science division in North America. And I left there after 22 years, joined Turning Point Brands in 2006, and was head of all of their—was a senior VP of operations there, where I headed up all the science, R&D, quality, operations, and logistics there.

I joined Streamline 2 years ago to help them with their strategy, focusing on trying to understand and adapt in this heavy regulated market and how to potentially not only survive but thrive in this particular market that we're in. So, I'm glad that you're having this for small manufacturers. I've been on both the big manufacturer side and the small manufacturer side. I think I have an understanding of the challenges from both sides, and I appreciate that Lowell Zeta and the CTP put this together today so that we could have some input into how we move forward together.

Steven Przybyla:
Morning, everyone. I'm Steven Przybyla. I'm a board member of a company called IKE Tech. IKE Tech is a technology solutions provider in the nicotine space. In April, we submitted a component PMTA for a hardware and software solution related to age gating at the point of use using biometric technology. We had great discussion around that, and I think today, I'd like to bring to light, you know, some challenges we had pre-submission and now post-submission, relating to software understanding that, you know, post the FDLI meeting in October, it seems to be the position of the agency that if you want to use flavors, you might need to employ age gating at the point of use to get those flavors approved.

We want to be part of the solution here. We want to protect youth from accessing these products. We want to be able to provide good products to those looking to transition off of combustibles into reduced risk products. So, thank you to the agency for inviting us here today for this discussion.

George Jawlakian:
Good morning, everyone. My name is George Jawlakian. I'm the compliance director and general counsel for Fumizer, LLC, and here on behalf of them today. Fumizer is established in 2010 in California as a manufacturer for open container e-liquid products. Since then they've grown to about 100 employees now, exclusively focusing on the manufacturing of bottled e-liquid products and have been involved in this PMTA process ever since its fruition. So, thank you for having us here today.

Todd Cecil:
Thank you very much. All right. With that, let's go ahead and open up the floor. Please keep in mind this is intended to be a roundtable. You can answer each other's questions. You can jump on other people's questions. This is—it's not intended as a Q&A per se. So, feel free to—if anyone wants to start the discussion with questions or comments, feel free.

Charles Melander:
Well, I'll go ahead and start. I have a comment and a question. Thank you.

First, it seems like there was a common theme from the last panel that providing standards around product characterization would be extremely helpful for small manufacturers. And the reply that I heard was that product standards from CTP's perspective are difficult. But I think in the manufacturing controls section, that it somewhat sets a standard for how we're supposed to operate with QMS, ISO was referenced in there, [unintelligible] is referenced in there. So, it somewhat sets a standard that we can follow when it comes to how to do the manufacturing of these products. And so, I just—I think that there's an opportunity here that if we could apply some of this thinking to the other sections that it would be very helpful. So, I want to applaud you for—on the manufacturing controls—trying to provide some clarity and some, what I would call so-called standards around how to do manufacturing. So, I want to applaud you for that.

My question gets back to something that has to do with clarity and cooperation and communication. And I know that in my experience that other governmental agencies have tried to work with industry to help them comply, especially on the manufacturing side. And as an example, OSHA, they actually promoted that they would—that you could invite them into your manufacturing facility. It wasn't an audit or anything like that, but it was a way for them to come in and point out ways that you could actually comply and help your manufacturing make sure that you comply with the OSHA regulations.

And so my question is this: Is this something that FDA is open to, instead of just coming in and doing an inspection, to actually allow industry to say, can you come in and do a unofficial inspection and help me understand what you are looking for and making sure that I'm able to comply with your expectations?

Todd Cecil:
Thank you very much. I think that we can say, I—they're tossing to me—yes, we absolutely can. We have done it in the past. We do go out and visit. It's not an inspection; it is a visit. We would have to put something in the Federal Register requesting people to send in a request to an invitation for us. We have not done it in a number of years because, number one, we had 27

million applications that came in, and we were a little overwhelmed in trying to get all that work done. So, we have not been able to do that to the degree we would like to. We are certainly interested in doing that. And we will have to post something in Federal Register at some point so that we can reinitiate that process again.

Charles Melander:
And I would really appreciate that because having been in this industry a long time—I age myself here, but having been in this—in what I consider harm reduction for a long time, Swedish Match was very focused on harm reduction. Turning Point Brands was focused on harm reduction. And I've pretty much spent my whole career trying to provide products that were less harmful than combustibles. I really like to hear that. And the reason I like to hear that is because I think that as small manufacturers, on the manufacturer—not only the manufacturing controls, but the other sections of the PMTA is that we're looking for more of a collaboration rather than—in having a dialogue and being able to help public health by providing products, getting through the PMTA process, and providing products that are good for public health. And this could be a first step for us to actually start working more closely together, I think. And maybe if we can take this and build upon that to where small manufacturers can actually work more closely with you and get through the process, I would really appreciate that.

Matthew Walters:
Just to comment further, we had opportunities to do that in the past, especially, I've been here for 15 years. And so, it's been—when we did those opportunities, it was quite informative for me as a new scientist at FDA, to understand tobacco regulation, to understand your processes and how those worked. We treated those more as an educational opportunity to inform staff. So, just a comment that I always thought those were very helpful, so.

Charles Melander:
Thank you for that. Thank you. And education on our side and education on your side. Thank you.

Bryan Burd:
And in the roundtable format, if I can comment on Chuck's comment here. He mentioned the companies he's with, and they were focused on harm reduction. I do want to add, you know, many of the small businesses we've been involved with also focused on that. The—there was a—the Director of the CTP—Acting Director Bret Koplow, was at a FDLI conference, October 29th, and he threw out a statistic which is—the CDC has out there, but 480,000 people die annually of cigarettes or cigarette-related diseases. And I think that's a main focus. And I would hope that that—that's always been our guiding principle is how do we address these half a million people dying every year of something that's preventable. And it gets a little frustrating that, you know, we believe we've got solutions or the companies that we work for have solutions to address these potentially preventable deaths. So, is that—I guess to throw it into a question, is that something that we're—the utmost importance or the top thing that we can align on?

Todd Cecil:
Again, we are absolutely aware of the potential benefit from products. Now, we have seen products applied to us that have got substantial risks, some of them perhaps as big as cigarettes.

So, we have to look at every one of them and consider each one of them individually so that we can ensure that we are not putting our cigarette smokers, who are hopefully quitting, and we're hopefully helping them provide a way to go to a safer approach. But it needs to be safer, and it needs to be demonstrated to be safer. And that is a big piece of our assessment of APPH is how do we protect the public people—public.

So I did also want to also bring up the question about standards, and I think that you raised a great question about standards. And I did want to point out that, well, I spent 20-odd years at USP. Standards are important to me, and creating standards so that we can help the industry is very important. We do work actively with CORESTA and have worked with CORESTA for a number of years. We do actively work with ISO and have worked with them for a number of years. So, we are trying to find ways to build a—standards that help the industry with the industry. It has been, again—the last couple of years been a little bit difficult. But I think that is something that we're hoping to get back to doing more of because we feel that it benefits you all. It certainly benefits us in that we get information out to you to the degree that we can.

Charles Melander:
Great. Can I just build on the CORESTA because I had a question about validation, method validation. If the method has already been validated through CORESTA and/or AOAC or any of the other bodies out there that validate methods, is that something—as long as we follow that method, is that something that's acceptable to you rather than us doing our own method development and trying to create our own method, interlaboratory, intra-laboratory validation?

Matthew Walters:
Yeah. If you're using a ISO or CORESTA method, analytical methods, I'm talking mainly here, that is acceptable method. We obviously would need to make sure it's verified in the laboratory. But if it's a internationally recognized method, went through all the round robin testing, that is acceptable method. Again, you just need to verify that can be used in the laboratory, so.

Todd Cecil:
And for your specific route of administration.

Matthew Walters:
Yeah, and—

Todd Cecil:
Materials.

Matthew Walters:
—analytes and the matrix.

Todd Cecil:
Now, I also want to come back to Bryan's question about transparency. I know that we did a recent pilot using nicotine pouches. And Ben will be up here later, and he certainly was a big part of that. And we did do a much more transparent approach to try to get out in front of people and talk to the companies to help things move along much more quickly. We are in the process of

looking at how that can be used for ENDS products. We don't have—we've got some lessons learned, things that we're working on. We have not implemented it at this point in time, but it is something that we are considering and trying to find a way to build in more communication and more transparency as we work through these applications. So, no promises, but it is something that we are absolutely working on.

Charles Melander:
Could I ask a question about that?

Todd Cecil:
Sure.

Charles Melander:
I'm intrigued by your comment, and I was intrigued by the pilot program that you did for pouches. Would FDA—obviously, we have a lot of—going back to what we just talked about which was on manufacturing. When we invite you in, you learn things. When we learn things—it seems like, in my experience with other agencies that, you know, the collaboration helps both of us.

So my question is this, you've had some experience with the pilot program with pouches. Would you be willing to work with small manufacturers—who I think have a lot of experience in this area and are really trying to promote public health by providing products for smokers. Is there a way that we could have—before you define what this is, that we could have some kind of roundtable around that to where we could provide some feedback on our experiences and how we believe that these are some of the approaches you could take in order to have a more streamlined or pilot program around this?

Todd Cecil:
Putting together a roundtable does take a lot of time and effort. And so, I'm not saying no, but I'm saying take advantage of the docket. Give us some ideas, give us some information, post it to the docket. We are reading all of those. We will continue to read them. I think it'll be open for an extended period of time. So, please, reach out with some of that.

I would also recommend pre-review meetings. Arrange with your RHPM to come in and present what it is that you're manufacturing. We look—we can come in. We'll listen to what you're offering in terms of the products that you've got, especially if it's a novel product. We are always—appreciate the opportunity to understand, see what it is, understand what it is. It helps us with our application. So, I would recommend that you reach out to your RHPM about a pre-review meeting.

Bryan Burd:
And, Todd, thanks for mentioning the transparency. You know, one of the things as representing small businesses, the resources are limited. So, stability testing, developing work instructions for every procedure, there's lots to do. You know, I look at these slides, and if you look in the bottom left corner, it says this is not a formal dissemination of information and doesn't represent the agency position or policy.

And what I often struggle with is, you know, Karen talked about something on the testing, you know, make sure that you test the products under abnormal or misuse conditions. Sounds great. But when you're allocating your testing dollars for stability, it gets difficult to understand what's noise, and what's a requirement, and how can, moving forward, we get rid of this disclaimer, and this is what you should do, and not it doesn't represent our position.

Karen Coyne:
So, the disclaimer is because this is not a rule. So, this is informational session. So, yes, having SOPs and work instructions, getting COAs, that takes a lot of effort. What we need—those are the most common ways for us to understand your manufacturing process. So, I'm not as concerned that you have a separate SOP and a work instruction. The work instruction can be part of the SOP.

What we need to understand is how you manufacture your product. So, SOP is the most common way of doing that. If you provide detailed instructions without calling it an SOP, I'd be okay with that. That's the most common way, is to follow 9001 and have the SOPs. We need to know what equipment you're using, who's doing the thing so that if somebody new comes in and they're making your product, mixing your e-liquid, assembling a device, it's the same each time. And so, we just—we need that step-by-step instruction.

Bryan Burd:
And I get that. I guess more on the testing side, so—

Karen Coyne:
And so, for that abnormal—

Bryan Burd:
That but, you know, there's information out there looking for, say, three batches, do seven reps each. Each, you know, stability time point, should we do HPHCs at TN? Just trying to cut through—again, a lot of small businesses, it's a very finite amount of money that they can allocate for this testing or—not can allocate but understanding what's truly needed versus what is a recommendation or—you know, if you've got strong results in other areas, it becomes a challenge to know what's appropriate and how far do they have to go in each area.

Karen Coyne:
So, you mentioned specifically, stability and time points. Is that what you're—

Bryan Burd:
In this particular case, it is. Do they need to do seven reps on three batches? If we're going to ask a specific question.

Karen Coyne:
So, that sounds like a chemistry-related batch testing. I think that's generally—I'm not a chemist, but I think that's generally what is used for—oh, go ahead, Matt.

Matthew Walters:
I mean, that's what we believe is best practice. That being said, if you believe that, say, five is sufficient, we need a rationale and explain why you believe five—we don't need seven. My message, I keep on saying, is provide the rationale, explain, and I think that really goes a long way for FDA. So, you know, I'm sure you're talking about the validation guidance where we have some of that in there. That's what we believe is best practice as a guidance. You don't necessarily have to follow. We obviously would like you to follow it. But if there—if you have a different approach, you know, I think just justifying, explaining is what's important to us, so.

Steven Przybyla:
The—I'm sorry, Bryan, I didn't mean to jump in here. And I appreciate your comment. But the unknown, to small manufacturers, is critical. Because we could provide all the scientific rationale in the future, if you don't accept it, it's death for us. Okay? And that's where it becomes a very—so, what would a small manufacturer do? Well, I'm going to do 7,3 because I cannot afford to do 5,2 or 5,3 and have it come back as RTF or MDO. And then I got to start all over again. So, this is the paradigm we're in.

And look, I understand what you have to deal with when it comes to regulation and the things that you have to deal with, but walking in our shoes, okay, if we don't have certainty, we have to then go with what we know, because we cannot afford to have a no. We're out of business, or we just invested $2 million in a application that gets denied, and because we don't know, you're going to tell us why. Okay?

And if we had a process to where, hey—as an example—you did 5,2 and you gave the scientific rationale. Okay. You did all the statistics, and you show that the variability was just—was not going to be any more than in the 7,3. But that's not—there's something wrong with what you did.

Okay. As an example, if we had the opportunity, I know there's a deficiency letter. Okay. But sometimes you don't get deficiency letters. Sometimes you get a no. And that's where—going back to communication, collaboration, understanding each other. That's what I think, as an industry, that we would prefer is that if there's an opportunity—we want to do the right thing. We want to fix the it if we can. But sometimes we don't get the opportunity to. Okay? Sometimes we get—we don't get a deficiency letter. We'll get an RTF, or we'll get an MDO. And you'll explain why, but we don't—we've got to start all over again. And we can't afford it.

I mean, we don't sell cigarettes and make billions of dollars a year. Okay? We sell—we are committed to saving the lives of smokers not selling smoking products. And that's where there's this somewhat problem with us as small manufacturers and trying to get through the process.

Todd Cecil:
Well, we want to keep in mind, when we talk about RTF, if you've gotten an RTF, it's because the core pieces of information that have to be there are not there. We cannot begin review. We are incapable of actually getting into this—the full scientific review. If you get a deficiency letter, absolutely, there's gaps in data. We're looking—we're actively seeking responses to questions. We also have found in many cases that we'll get partial responses back for deficiency letter. A deficiency letter is these—the things that we have concerns with. We need more

information. We don't always get answers, and it makes it very difficult for us to say yes despite the fact that we'd like to. If there are a lot of deficiencies, and there often are, and it's a short time frame to get those things returned to us, we do need to understand what the issue is, and can we get the information from you? What is getting in the way of that? And that's what this discussion was sort of about. What is it that we can try to do on the manufacturing control specifically, already done the other, and that we can find ways of helping make it clear what we're—what you're missing and why you're missing it.

And I think Karen has been pretty clear on we need to understand what your product is. We don't see it. You guys have been working with it for years. You know exactly what it is. We don't see it. All we've got is the picture that you've got in there if you give us one. Even the biggest manufacturers don't give us the pictures of what this thing is. So, we don't understand what we're looking at. All we have to go by is the description and the data.

Charles Melander:
Well, and that gets back to a question on manufacturing controls, which I think you want to get back to. Okay. So—

Bryan Burd:
And I'll just add, Chuck—sorry.

Charles Melander:
Yeah.

Bryan Burd:
In June of 2025, you released some internal memos about ELCR. Those were well received by small businesses. So things like that, any kind of communication that you can provide, these are great. Although the disclaimer, I know you got rulemaking, but that's welcomed information, small businesses.

Charles Melander:
Yeah. No. So, you mentioned that there were—you listed some common issues with manufacturing process descriptions that you saw some common errors. So, my question is this, if you find these, what process do you follow after you see that?

Karen Coyne:
So, as a reviewer, if I see an issue with the process, if I'm not understanding how your product is being made, that would translate into the review and an evaluation of limitation or deficiency. So, if it's a minor thing that we don't fully need to understand—and I'm blanking on what would be a minor thing, and I know you like examples, but that would be a limitation. If it's something significant, if we don't know how you're mixing your e-liquid, if you—we've seen where whole process steps are not included, groups of SOPs, that's a deficiency. We need to know how you're making your e-liquid.

Charles Melander:
Okay. So, we would be getting a deficiency letter.

Karen Coyne:
Yes. You would get a deficiency letter.

Charles Melander:
Okay. Okay.

Todd Cecil:
And let me add on to that.

Karen Coyne:
So—

Todd Cecil:
Oh, go ahead.

Karen Coyne:
I was going to say, with the new process, with the pilot, there were increased communication. So, if it were something like, we're missing some SOPs, that could be communicated during one of those phone calls so that you would have a chance to amend your application and send us those SOPs before you get a deficiency letter.

Steven Przybyla:
This is an important point actually, because software doesn't fit neatly within the manufacturing controls, I think, we've been discussing today, right? And I think with—given the emphasis on age gating at the point of use and having digital solutions to prevent youth access, just reflecting on our process, there were questions pre-submission, I think we had a great pre-submission meeting. There's now questions post-submission on how we can keep the software up to date, add features, et cetera, without blowing the actual submission that we made and needing to amend or submit a new PMTA.

Does the agency plan on putting out guidance for software in ENDS products, and, you know, will that guidance rely on direction from other centers? Will the agency—will CTP, you know, lean on CDER and others, or will it create its own guidance? You know, has there been any thought given to that?

Karen Coyne:
So, software is definitely different from other components. We don't currently—CTP does not currently have guidance on software—what you should be providing, but CDRH does have. The Center for Devices and Radiological Health has guidances on software and what to include and what to consider if you are making updates and if you had the external meeting request that was probably referenced in the response that you received.

Steven Przybyla:
I think that's helpful. I guess there's no other, really, place to ask this. So, I'm going to ask maybe two off-topic questions. Given the focus on age gating, you know, with the director's remarks,

how does the—does the center look on amending PMTA applications to include age gating at the point of use? Will those applications be moved to the front of the line? Will they go to the back of the line? You know, do you look favorably upon that? I guess that's—I'll stop there.

Todd Cecil:
At this point, again, we're talking about manufacturing control. We'll take that under advisement. We'll see if we can get an answer to you. I don't think that we—it's difficult for us to know—to move things around in the line depending upon when things are submitted. Adding software, again, so long as it's in the application before we start, there's no problems. If there's changes to the software, changes—if we're in the middle of reviewing, it means we end up going back and starting over again, but—which we try to avoid because it makes for a longer review time cycle. But I hear you, and we'll take it back.

I did want to also come back to—respond in part to Chuck on a—when you get a deficiency letter, if what we've asked for is not clear, you can ask clarifying questions of us. So, you can send in a response and say, here's—I didn't understand what you needed with this. Can you give me more information?

We obviously—we often get clarifying questions that say, if I make this change, will you say yes to me? That's not a clarifying question. That's a review question. But if you clearly—if what we wrote is not clear to you and you don't exactly understand what we're looking for, ask a clarifying question. Work with your RHPM, get the questions into us, we will respond to them and get you those answers so that you can prepare the materials that we need.

I want to go to George because George hasn't gotten a chance to say anything. I may regret that, but I—

George Jawlakian:
I appreciate that. Thank you. As far as the question that I was pondering was more so related to that risk mitigation testing on the abnormal and misuse conditions. So, as an open tank e-liquid company that doesn't have any involvement with devices, it's—you know, it's—there's been testing on products, and then, you know, the initial product that we chose went out of business. So, we did a comparator. We started with another product, and, you know, it's—as far as with the budget constraints, like Bryan was discussing earlier, becomes impossible to try to figure out how many products is enough to test as far as devices go. And I guess I should ask, is there an expectation that the e-liquid products will work across the board in all devices, or is there any kind of guidance in that?

Karen Coyne:
I think you would best know what types of devices your consumers are using your e-liquids in, and I would recommend that you test a range and to show—so, for instance, if they're used in high temperature or high-powered devices, test at a lower power and a higher power or a lower temperature and a higher temperature, to show what happens with the HPHCs and any other characteristics of the e-liquid. And then, as we've mentioned multiple times, provide a rationale which—the scientific rationale for why you're choosing your low power or high power. The risk analysis, the misuse, I think, is different if you are selling an open e-liquid versus like a pod.

George Jawlakian:
Sure. And, you know, as we've gone through that process, but it's—as new devices are coming out or they're having significant changes as is, you know, is it safe to say that as long as we put our disclaimers on which specific products are—settings to use a product on, is that enough for us to be able to—you know, even assuming—I mean, not assuming, but we have gone through and spoken to the customers and seen what the majority of them use as devices and then tested those devices and—you know, is it possible to disclaim ourselves to protect enough, to see that as a—you know, to start removing those variables, or is it still across the board as everything just needs to work?

Karen Coyne:
I would say it's up to you to provide that scientific rationale for what you're testing and that it really does come down to a review issue. E-liquids are a lot different than selling a pod. I would say, yes.

George Jawlakian:
Yes, as in enough or—

Karen Coyne:
Give us the—

Todd Cecil:
Yes, both.

Karen Coyne:
It's okay—use the devices that you're expecting your customers to be using and provide the scientific rationale for how you chose those devices to give us the test data on your e-liquids.

George Jawlakian:
Understood. And I do have a follow-up question to that as well. So, as of right now, you know, it's—the products have been tested with devices that are popular in the market. But say there's a new device that's an MGO—that receives an MGO and that becomes now the standard, right, as far as an open tank device. If our product doesn't work well with that one device that's received an MGO, does that hurt us as far as an e-liquid company, say it doesn't test well at all with that device, and that's the only one that has an MGO in the market now?

Karen Coyne:
I don't think it would.

Todd Cecil:
Yeah. Again, the expectation is not that everything gets authorized now. You need to test against it. And then each time you test against it, I think the intention is you build your application, tell your story, use the—a worst-case scenario that was available to you. And we took, you know—when we talk about cigarettes, we talk about standard puffing and intense.

We say you should do your testing in standard and intense for e-liquid, but we don't define what intense is. And we don't do that on purpose, but in many cases—I mean, take a look at people and how they're using it. Are they taking five or six puffs within a couple of seconds of one another rather than allowing the device to cool back to room temperature before you use it again? And that's an intense application. You have a higher temperature that's going to affect your HPHC yield significantly.

So, I think those are the sorts of things you want to be thinking about when you tell us, here's what we did and why we tested it using this device, and here's how we looked for a more intense, more worst case scenario. So, now we have comfort that you are doing testing using a situation where we can have a better understanding of what could happen in misuse situations, right?

George Jawlakian:
And I appreciate that response, but respectfully speaking, is—you know that standard, which I understand the FDA's rationale, but, you know, when we were doing our testing, it was against traditional cigarettes. And then, you know, when a closed system tobacco device had received an MGO then the standard did change to ensure that our products, our flavored products are testing against that particular product. So, it's—I guess as far as the concern with the device too, is I could see the FDA's rationale of stating that this is a product now that has a marketing order, so its compliance has to shift. And a concern from an e-liquid manufacturer is, if it doesn't work with that product and then, and then what?

Todd Cecil:
I would say we consider each application independently. We recognize, obviously, in 2020 when we started getting applications for ENDS products, there were no authorized products. You have to tell your story. It does not—it is not appropriate for us as far as I'm concerned. But this does not represent a formal dissemination. But it does not make a lot of sense for you to go back and retest and retest and retest every single time. Tell your story based upon why you did what you did.

If we aren't happy with what's in there because it doesn't cover things well enough, we'll have a deficiency. We'll let you know that, you know, well you didn't do X, and we need some more information from you. But I don't—I would not expect—I do not believe that we have any deficiency letters saying you didn't test versus this XYZ product that we just authorized. To my knowledge, we've never sent out a deficiency like that and that is not our intent. Your application is your application. It's your product. Comparative products are something we use for comparison to get a feel for where you live within the broad context of the other products that are out there. But it is your product and your product alone that we are assessing.

Charles Melander:
So, can I make a comment on this subject? Open systems are unique, obviously, right? Disposables are not, because it's one system. You can test it. It is what it is. But open systems are unique. E-liquid manufacturers should not be responsible for what the hardware does to their product, and the hardware should not be responsible for what's in the e-liquid. Okay? Hardware should not be responsible for what's in the e-liquid, but they've gotta test e-liquid, right?

Todd Cecil:
Yes.

Charles Melander:
And on the other hand, e-liquid should not be responsible to what the device is doing to their e-liquid if the device has very high temperatures or has some problems with it, right? Okay. So, there's this paradigm here that is very difficult for us, as small manufacturers, to try to figure out. Now, I'm going to give you an example that does exist, which is the Kentucky Reference Cigarette. Okay? You have a standard product that you compare cigarettes against. Okay? I don't under—and so, there is something that you already have done. It may have been done before CTP, but it was—it's been done. Okay?

And I just want—I just want you guys to understand that as small manufacturers, we have limited resources. And going back to what Geoff said earlier is we have a lot less resources than we could have because of the unknowns of this process. Okay? There—it's very difficult for an investor or anybody else to say, you know what, if you do this, we're going to invest in you because you're going to do this, and you're going to get through. Okay? That's just the way it is.

So, my point is this, is that with limited dollars, if we could have—and this is where I go back to standards again. But if there was a hardware standard that said you can't go above this temperature, or if there was, hey, if you use a device that doesn't go above this temperature, doesn't have these metals in it, whatever, because guess what, the metals come—you don't know if the metals are coming from the device or coming from the e-liquid, and you use that device, you can go ahead and test your e-liquids, right?

On the other hand, the hardware guys, you know, if—going back to something else, which is if it doesn't contain this stuff on the e-liquid side, you can use this e-liquid in your hardware, and you can test it, and we will approve or disapprove your hardware based on those results. I'm just giving you an example of the issues that we're trying to face as an industry when we're trying to figure this out. And I know you're trying to figure it out too, but what would be very helpful, just—if you just start with a premise of e-liquids should be responsible for what's in there and what they create during aerosolization. And hardware should be responsible for what's in there and what they create during the heating process.

If we start there, maybe we can figure something out here, to where both of us can actually have something, that we can actually figure this out, because we—I understand you want test with this, test high and low. We don't know what is high and low, and we don't know whether it's—whether that's really what consumers—by the way, there's nothing been approved yet. So, we don't even know if that's even going to be on the market in the future because it may not be any good according to your standards. So, anyway, I'm just giving you some feedback on something that would—that we have to deal with all the time.

Todd Cecil:
Absolutely appreciate it. That is something that we are considering—have been considering. Hopefully, we'll be seeing—you'll be seeing something—they'll be asking some more questions of you all in the not too distant—the FDA soon.

Bryan Burd:
Before you wrap up, Todd—

Todd Cecil:
Yes, sir.

Bryan Burd:
I've got a quick question. So, something very uniquely—unique challenge for small businesses is the supply chain. And there's dozens and dozens of vendors that they're working with. There's a very delayed process. It has been—to get approval and change control. And so, if a cotton manufacturer goes out of business or they've got to switch that or some piece in the device, pharma has guidance. Devices have guidance. Is there some—what would be great for us is if there was some guidance on change control. Steve mentioned age gating, you know, even that, is there a—I mean, for safety reasons or something like that would be fantastic.

Todd Cecil:
Absolutely, yes. A scale-up of post-approval changes type of guidance would be a wonderful thing. We're not there yet. It's something we are certainly interested in. We have been talking about it. Again, it comes down to—there's a lot of guidances you've talked about us creating, and we would love to do all of those. But we also have a few reviews that need to get done. And so, it comes down to prioritization and—but I can promise you, we will take away what we heard today and hopefully be able to give you something sometime in the future. I cannot promise you when that might happen, but I can promise you that it is lunchtime.

So, with that I want to say thank you very much to our panelists. Thank you to my colleagues from FDA. And I—hopefully, we can continue this discussion further and—at lunchtime and thank you so much. Be back here at—oh, I need to find my schedule—12:50. All right? 10 minutes to 1. Thank you so much.

[break]

[music playing]

Lynn Hull:
Okay. All right. I think we're ready to get started again. Everybody's ready. All right. So, welcome back from the lunch break. We are now going to start Panel 3, Pharmacological Profile.

And so, just a little introduction. One of the most important aspects of FDA's evaluation of APPH for a new tobacco product focuses on the abuse liability of the new product, including the delivery and uptake of nicotine by a user of the product. Nicotine exposure typically is evaluated through clinical studies that evaluate nicotine pharmacokinetics after use of the new tobacco products. And similar to some of the questions this morning about bridging, you know, occasionally, it is possible to bridge the findings of one ENDS product to another. This allows for a reduction in the number of studies needed to support a product.

However, the proper design of these clinical studies for ENDS products can be complex and needs to be highly developed before work is initiated. This roundtable will address criteria that could improve the quality of the clinical studies for ENDS products submitted by applicants and provide participants an opportunity to ask questions about design basics to inform their applications.

So, first, I'd like to introduce our FDA presenter, Dr. Carolina Ramôa. Dr. Ramôa serves as a supervisory pharmacologist in the Division of Individual Health Sciences in CTP. In this capacity, she leads a team of Ph.D.-level scientists in evaluating tobacco product applications and conducting regulatory science research. Her scientific expertise is in addiction and behavioral clinical pharmacology tobacco with extensive experience in regulatory science. Prior to FDA, she gained international experience with the World Health Organization's Tobacco Free Initiative in Geneva, Switzerland. Welcome, Dr. Carolina—oh, Ramôa. Sorry.

Carolina Ramôa:
Hi, everybody. Thank you for the kind introduction, Lynn. I'm here today to talk about the pharmacological profile of tobacco products and how we use that data to evaluate abuse liability and addiction.

Okay. During this presentation, I'll detail some outcome measures we use to evaluate abuse liability of new tobacco products. I'll talk a bit about how to design these studies, hone in on relevant participant populations, and review product bridging.

Abuse liability refers to the potential of a substance to result in addiction and be used repeatedly or even sporadically, resulting in undesirable effects. Addiction is chronic—is a chronic relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences.

The abuse liability of a new product is important for FDA to evaluate because it indicates the degree to which users of the tobacco product are likely to use and develop an addiction to the product. Abuse liability may result in craving of the product and compulsive and continued use despite harm or risk of harm and may also indicate the likelihood of product switching. Now, we can't talk about addiction and tobacco products without talking about nicotine.

Nicotine is the primary addictive substance in tobacco products. The rate, degree, and total amount of nicotine delivered into the brain significantly impacts product abuse liability. Behavioral and clinical pharmacology, or BCP, assesses abuse liability based on the totality of evidence, with product-specific clinical studies providing the strongest evidence. A clinical study measuring nicotine pharmacokinetic outcomes gives us data to directly evaluate nicotine exposure. I'll go into more detail in the following slides.

Nicotine exposure is a critical piece of information and one of many outcome measures that go into an abuse liability evaluation. The most common clinical study design to support an abuse liability evaluation of new products is a multi-session, randomized, crossover study comparing the pharmacokinetic, or PK, profiles, meaning quantifying nicotine exposure of several nicotine concentrations and flavors of a new product to comparison products with a known abuse

liability, for example, combustible cigarettes.

Ultimately, the totality of evidence evaluated by the FDA includes both quantitative measures as well as qualitative measures. Qualitative measures account for human behavior, which is not always predictable. For example, knowing the nicotine concentration of a new tobacco product is insufficient to generate an abuse liability assessment because human behavior or how participants will use that new product is difficult to predict. Abuse liability evaluations account for the intersection of quantitative and qualitative measures.

Next, I'm going to walk you through an example of a pharmacokinetic study design. This example will be referenced later when I walk you through two hypothetical product bridging examples. In this study, participants would visit the lab five times. During the first visit, they would undergo screening, participant consent, and randomization. To increase—sorry, to increase—to decrease use biases and extraneous variables affecting the results, participants are randomized across the new product conditions and comparison product condition.

In this example, the comparison product is a participant's usual brand cigarette. Cigarettes make a good comparison product here because they are often used by end users and have a well-known high abuse liability that helps the FDA evaluate the yet unknown abuse liability of new products by comparing the outcome measure of each experimental condition.

Each of the remaining laboratory visits, Visits 2 through 5, participants come to the lab, are given the study product, and use it for a prescribed use session, or Phase A, followed by an ad libitum use session, or Phase B. To clarify, both Phase A and Phase B take place during each subsequent lab visit. During the prescribed use session, participants are directed to take a certain number of puffs, for example, 10 puffs separated by defined inter-puff interval like 30 seconds.

During these sessions, blood samples would be taken at predetermined time points to later be evaluated for biomarkers of exposure including nicotine. Questionnaires would be administered to evaluate subjective effects such as liking, and puff topography measures such as puff volume and puff number would be recorded to further evaluate product use behavior.

Next, I'll highlight some common outcome measures from these studies. Dependent on the design and timeline of a clinical study, we have a window into acute nicotine exposure or chronic nicotine exposure. In an acute exposure setting, as described in the previous slide, in Phase A, a participant goes into lab for a prescribed use session where they take 10 puffs from a new tobacco product, and their blood is drawn during regular intervals. Those time points are reflected on the X axis of this graph. Their blood plasma is analyzed for nicotine concentration reflected on the Y axis of this graph, over time generating a pharmacokinetic curve or PK curve.

The measure derived from this curve include maximum nicotine concentration reached, the Cmax, and the time it takes to reach the Cmax, the Tmax. These characterize the rate of nicotine absorption. Additionally, the area under the plasma nicotine concentration versus time curve is the AUC parameter and characterizes the extent of systemic nicotine exposure or total nicotine exposure.

Chronic abuse liability studies evaluate tobacco product use over the course of more than a day, for example 5 days, and include outcome measures like urinary or blood nicotine exposure measures of nicotine and its metabolites. The location of product use can vary, typically in a confined inpatient setting via several in-person lab visits or outside of a lab.

Subjective effects of a participant's use experience are self-reported and collected through validated questionnaires. This is an example of a question a participant may see. They would be asked to report on a 0 to 100 scale how strongly they agree with the idea, quote, I have a desire for cigarette right now, end quote. Other questions include themes like relief from withdrawal symptoms, liking, and willingness to take again. Self-reported ratings of these subjective effects are evaluated and compared across experimental conditions. The answers to these questions can be used to estimate reinforcing effects and, with other outcome measures, to estimate the abuse liability of tobacco products.

Use topography includes number of puffs, puff volume, and duration, and inter-puff interval or the time between puffs. Studies suggest that ENDS topography may change with user experience which may impact subsequent nicotine exposure. For example, people who are experienced using ENDS typically take longer, larger puffs and achieve a greater nicotine exposure, attaining a higher Cmax, compared to people with limited or no ENDS experience.

Applicants typically include adult users of either the category of the new product, for example, ENDS, and/or regular adult users of the comparison product, for example, combusted cigarettes. When selecting a comparison product, it's important to consider both the intended user population as well as the likely user population.

Prior experience with the study product or product category may affect interpretation of study outcomes and impact study confidence. For example, as previously mentioned, experienced ENDS users can achieve higher nicotine exposure from the same ENDS compared to ENDS-inexperienced users. It's also important to scientifically justify the selected participant population. An inappropriately selected participant population may decrease the extent to which the study conclusions are indicative of the new product's abuse liability in the intended user population.

Here, I'll highlight a few other considerations in clinical study design. Scientifically justify the comparison product selection. Consider the intended user population and the likely user population when making the selection. Consider the quality of the study and the confidence an evaluator would have in the validity of the abuse liability outcome measures. For example, insufficient sample size could decrease the quality of the study. Insufficient sample size could lead to an inflated effect size or misleading results. The quality of the study will contribute to the confidence in the outcome measures and how the outcome data will be weighed in the totality of evidence when evaluating abuse liability.

Because the abuse liability of a new ENDS is influenced by the combination of device and e-liquid characteristics, product-specific information like data from an abuse liability study using the new products, serves as the strongest source of information for an abuse liability determination of the new products. However, when product-specific information is not available

for every new product, applicants may attempt to bridge the data from the clinical study to the untested new products.

Bridging is a tool to utilize existing evidence to inform review of a new product lacking data. Bridging requires identification of product differences between the bridge products and an evidence-based scientific rationale describing these differences and their potential impact on abuse liability outcome measures. If bridging is inappropriate, those data will not be considered in the review of that new product.

Ideally, the applicant-submitted studies will include all of the new products subject to the review in the application. However, when the submitted evidence does not include all of the new products, for example, a subset of the new products, or evaluates products not subject to the PMTA, for example, study products with any differences compared to the new product, including precursor versions of the new product or different flavors, applicants may bridge data generated from the study products to support an abuse liability evaluation of each of the new products.

When bridging to new products, bridging information should include details and scientific discussion on whether and to what extent the differences between new and study products affect abuse liability measures including nicotine exposure, subjective effects, and use behavior, and scientific rationale for how the results of the study products are applicable to the new products.

BCP assesses applicant's bridging for differences in product characteristics, for example, nicotine concentration and device power; evidence-based rationale on whether, and by how much, product differences affect abuse liability measures; and whether the product differences might support a different abuse liability for the new product versus the study product. Many of these evaluations are conducted in conjunction with other disciplines like chemistry and engineering. We all work together.

Some product characteristics are known to influence abuse liability outcomes, and here's some not—but not limited to: nicotine concentration and formulation, product flavor, device type and power, PG/VG ratio, and free nicotine content. Consider individual product characteristics and the combination of total product characteristics of the new and study products in determining the appropriateness of product bridging. The more product characteristics that differ between new and study products, the more difficult and complex it becomes to appropriately bridge the products.

Clinical studies provide the most useful bridging information including nicotine PK studies and use behavior studies. Nonclinical data can be useful, such as machine-generated aerosol data or ingredient homology. At times, published literature may be acceptable when explicit rationale and justification as to why the products used in a published study can be bridged to the new products, considering the many characteristics that influence abuse liability.

In this example, a clinical study similar to the hypothetical mentioned earlier was conducted on three of the five new ENDS. In this example, all five new products are the same flavor. The only difference across the five products is the nicotine concentration. As you can see in the figure,

new products with 1, 3, and 5 nicotine—5 percent nicotine concentrations were tested for outcome measures like nicotine exposure, use behavior, and subjective effects. New products with 2 and 4 percent nicotine concentration were not tested.

To appropriately bridge from a subset of tested new products to untested new products, the applicant would provide evidence-based scientific rationale demonstrating that the outcome measures obtained from the tested products is also representative of the untested products. With regard to nicotine, the level of nicotine in a tobacco product may affect how the product is used. For example, it may affect use topography, frequency of use, and amount consumed, and therefore may influence dependence.

Testing too few products, for example, only the highest nicotine concentration or only the highest and lowest nicotine concentrations, may produce nicotine exposures and subjective effects that are not representative of the abuse liability and behavioral effects under the range of nicotine concentrations of the new products, remembering that each new product or bridging between new products is individually evaluated.

In this hypothetical example, the applicant elected to include low, medium, and high nicotine concentrations, representative of the new product line in their experimental design, which would be accompanied by testing nicotine concentrations of 1, 3, and 5 percent. The applicant could then bridge those tested products, 2 and 4 percent nicotine concentration, by providing use behavior studies that include puff topography outcome measures. Because the puff topography results demonstrate that the untested products are used similarly to the tested products, we would consider this adequate bridging. Again, this represents one hypothetical bridging approach that may not be appropriate for all applications.

In this example, similar to the previous, only some of the new products were tested. In this case, the only difference between the products is flavor. To appropriately bridge, the applicant would need to generate an evidence-based scientific rationale to demonstrate that the outcome measures obtained from the tested products is also representative of the untested products. Because the products are different flavors, the applicant would consider how the various flavors and flavor constituents in the new products could impact use behavior which could influence the user's exposure to nicotine. The applicant could consider the possibility that subjective measures of abuse liability could differ from each new product. These factors should be considered within the context of the intended as well as the likely user population.

In this hypothetical, an applicant tested tobacco, menthol, and strawberry-flavored ENDS of the same nicotine concentrations in their abuse liability study. They compared the nicotine PK subjective effects and topography of three flavors to describe variability in these outcomes as a function of flavor and how this variability compared to the data from the comparison product.

They bridged the results to blueberry and mint ENDS from their product line by assessing machine-generated nicotine aerosol yield from all flavors, and they included a justification of how the puffing regimen from the aerosol data is comparable to actual use via a topography study. They also provided an actual use behavior study to show that the frequency of product use is similar across tested and untested flavors. Again, this represents one hypothetical bridging

approach that might not be appropriate for all applications.

Those are all the topics I'll be covering today on abuse liability, PK study design, and product bridging. Since I've gone over a lot of information, I'll summarize the primary points here. Abuse liability information indicates the likelihood of users to become addicted to the product. Applicants should design abuse liability studies with consideration of comparison products, the intended and the likely user population, and methodological constraints.

Applicants should provide explicit product-specific information—sorry, justification to support bridging for any untested new product that are not evaluated in a study. Abuse liability evaluations are based on the totality of abuse liability information, the intersection of qualitative and quantitative data, with clinical studies providing the strongest evidence. Ultimately, abuse liability is one puzzle piece in a broader APPH evaluation that takes into account all scientific disciplines.

Thank you for listening, and I'll now be joined by Dr. Megan Schroeder, the Branch Chief of BCP, and we'll be taking questions during the panel session.

Lynn Hull:
All right. Thank you, Carolina. So, I'd like to, you know, start by—we've got introductions of Carolina and Megan—just to go through the panel, the rest of the panel, give you guys a chance to introduce yourselves where you're from and maybe a little bit of your background. Ed.

Ed Carmines:
Hi, my name is Ed Carmines. I'm here representing Charlie's Holdings. Charlie's Holdings is an e-cigarette and e-liquid manufacturer. I'm also the Chief Scientific Officer for a regulatory consulting firm called Chemular. There's a number of us here today from Chemular. And I've got about 30 years of experience in tobacco science. I'm a tobacco toxicologist—inhalation toxicologist kind of person.

Eric Heyer:
My name is Eric Heyer. I'm an attorney and a partner with Thompson Hine in our Washington, D.C., office. I'm here today on behalf of one of my clients, Maduro Distributors, which has pending applications for disposable ENDS products. I've been eyeball deep in e-cigarettes and ENDS products and PMTA since being involved in litigating the first e-cigarette case against FDA in 2009.

Steven Haddad:
My name is Steven Haddad. I'm the managing member of Breeze Smoke. We have several applications pending and a robust, comprehensive PMTA that's being worked on and finalized in the next month. I have 20 years' experience in the tobacco vapor convenience distribution space. And regarding PK, my knowledge has been in reviewing our own data plus comparator product study results.

Willie McKinney:
Hi, my name is Willie McKinney. I'm the CEO and founder of McKinney Regulatory Science

Advisors, a regulatory advising firm, as well as the owner and CEO of McKinney Specialty Labs, my lab that focuses specifically on nicotine and tobacco testing. And we do have validated methods for each matrix, by the way. But I'm here on behalf of Custom Technologies, which is a company that was incorporated in 2011, and they developed a very specialized e-cigarette and software tracking solutions exclusively for adult correction facilities.

The product was created to help jails and state prisons administrators address contraband cigarette tobacco within incarcerated populations where tobacco use rates are significantly higher than in the general population. The product has never been sold in the general public and is not associated with youth use. It's available only to incarcerated adults and operates within a fully controlled 24/7 environment, including jails, state prisons, and associated rehabilitation facilities. And I very much appreciate being included on this—today's panel, and I look forward to the discussion.

Char Owen:
Hi, my name is Char Owen. I'm the CEO of a small e-liquid manufacturing company. I have an engineering background, and I also do PMTA regulatory consulting and have been doing that since 2019.

Megan Schroeder:
I wanted to see if—maybe open up, see if anybody has any questions. Go ahead.

Steven Haddad:
If I can start, if that's okay. I want to—I'm going to zoom out to 30,000 feet if I can and talk about the concept of just doing PK studies in general, because I think for this portion of the industry, this is a very challenging topic. As you recognize, it's a—it's very expensive to do PK studies. They're complex to design. People want to make sure that they're designing them in the right way for their products.

And I kind of want to zoom out to the question of why are we doing these products and requiring them to begin with? I don't think anybody would contest that nicotine is addictive, right? And these products are obviously targeted toward people that use combustible cigarettes and more harmful tobacco products. And if we look at the list of HPHCs for ENDS, my hunch is that a lot of the applications that FDA looks at are—they're seeing multiple HPHCs below the levels of detection, below the levels of quantification, and they're probably seeing, by and large, fairly clean tox studies as well.

And when Congress enacted the Tobacco Control Act, the purpose, if we look at the statement of purposes and findings, was to reduce morbidity and mortality from tobacco products, right? And it seems to me that in—not only is this a very expensive requirement, a very demanding requirement, one that's hard to get right. It's got a Goldilocks problem of you can be—you don't know how you're going to come out, and you could be more addictive than a combustible cigarette and get thrown out. You could be not addictive enough, and people aren't going to uptake your product, and they're going to dual use.

And at the end of the day, this is already well known that it's addictive, and it seems to be much

more of a drug sort of evaluation and not anything that really goes to reducing morbidity and mortality from tobacco products. It's really studying a substance we already know is addictive. And so, how does this really advance Congress' intent in reducing morbidity and mortality? I mean, it just seems to me that if we're looking to find—to address the struggles that the independent industry has had here, whether you're a small manufacturer or even a large manufacturer, this seems to be a requirement that doesn't necessarily seem to be completely necessary or as fundamental to the APPH standard as other requirements would be.

So, that's my soapbox. I'll get off of it now. But that's what I want to throw out for discussion.

Lynn Hull:
Yeah. Megan, would you like to respond to that? No? Go ahead, Carolina.

Carolina Ramôa:
Hi. Thank you for the question. Can you hear me? Okay. I think that it's a very—it's a fair question that we all think about all the time, right? Like, we're trying to appropriately apply the TCA standards. But myself as a pharmacologist, right now, what I can answer is, how do you design something correctly? And I really hope that my presentation gave you some indication of that. And something else that I think that I encourage companies to take advantage of is our meeting requests. I've participated in those a lot, and those have generated wonderful discussions that are very unique to each product.

Each product is so complex. There's so many characteristics that we evaluate. So, it's really hard to give you, like, a broad answer, right? Like, there's more than just nicotine that influences abuse liability, and that's what we're evaluating. Ultimately, we are trying to take out Congress' direction with—through the TCA. It's absolutely what we're trying to do. I'm not going to discuss that further because I'm not a lawyer. I'll leave that to you. But in terms of designing a study correctly, like, there are avenues to engage with us on that before undergoing a very expensive study. And I think we all understand that, too.

Willie McKinney:
A couple of things. Earlier we heard about product characteristics, and I read a paper recently by Saul Shiffman, actually, on PBPK modeling, actually, or taking some product characteristics such as pH, PK, and aerosol mass, and determining where you are relative to a cigarette in terms of the PK, the Cmax. And he's not saying that you get a specific number, but you know you're well below. Why can't small manufacturers use that to help you guys know where they are, since nicotine is the substance that is most addictive?

Then secondly, I'll say, with your bridging approach, if I wrote down what you suggested, it was aerosol chemistry, it was topography, and then also an actual use study. I would just do the PK if all that is required to bridge, right? Can you guys comment on how we can simplify and have more communication and, maybe, lean more toward product characteristics to model and understand abuse liability? And I hear you guys are working on a PBPK model, actually, that could be very helpful.

Carolina Ramôa:

So, I'll go back to the point in the presentation where I talked about how we look at both qualitative and quantitative outcome measures, right? The intersection of those two types of measures is what I need in order to make an appropriate abuse liability evaluation. So, if you are able to give me both of those in different ways—PK studies are, like you said, it's the best way to do it. It really is. It gives me product-specific information.

But let's say if you have one product that's very similar to the other ones, right? Like there's one—we're going to go with the example of one characteristic difference. If I can probably—I can bridge from that product to another one if I know what the use behavior of it is, plus the machine-generated nicotine aerosol.

So, again, I'm always looking for product-specific bridging. It's got to be one to one. And I'm looking at all the product characteristics. If you differ in more than one product characteristic, it's going to become more complex, it's going to become more difficult. And then I'm also looking for qualitative measures like use behavior, like liking. I'm also looking for the quantitative measures like nicotine exposure, and I need to feel solid in those, right?

Like it's actually really hard. It's really difficult. So, I absolutely understand where you're coming from, where you'd like to make it as efficient as possible. And then I also understand where I'm coming from, where I have a duty to the American public to make sure I make a correct decision as to not impact them negatively, as to uphold APPH.

Char Owen:
Hi there. I've got a question, and he had mentioned that you guys are working on a PBPK model, possibly. If you are, it might be helpful for small business to have access to that. Or if they've developed their own, is there a collaboration pathway which they can use to validate their methodology so that it would result in a more robust application?

Also, in your presentation, I noticed that some of it was user experience, and that's what you use to bridge some of those gaps. As a small e-liquid manufacturer, my experience has been that their previous use of nicotine, their—how their body is structured, all that is highly—highly affects what their experience is going to be. So, even—and that's going to change from group to group, and I can't determine what that's going to be. I could take a guy who's never been exposed to nicotine before and his experience is going to be completely different than someone else. So, I understand the model effect is great and I understand that effect is great. I just don't know about the efficacy of the user experience added to that that it's going to be solid data.

So, one, is there a collaboration pathway that those conversations can happen between us? Because obviously what my experience is—as a manufacturer is different from what you guys are seeing in study data. Because, you know, I see those people every day. We've helped thousands of them stop smoking. We, as small business owners, have that data. We have those life experiences, we have that. And so, I don't think I would design the study that way is what I'm saying. So, is there a pathway—a collaboration pathway that we can have between the FDA and small business to answer those?

Megan Schroeder:

Yeah. I think regarding the collaborative pathway, I think the best way to do that would do a meeting request so that you can present your data. FDA can read over it, study it, and provide you direct responses to your specific data, the specific model inputs, and things like that. That's what I would recommend for that.

Char Owen:
In the past, we've had those meetings and they have resulted in letters that come and say, "See guideline such and such" and it doesn't get us very far when it happens. And it's very determined on what person you get in your meeting. We do listening sessions and we get exactly that they listen, right? So, in this kind of a thing we really need intensive back and forth feedback. So, is there any collaboration pathway, in other words, that has parameters that, in other words, we're not going to get told, just go back and see the guidelines, we're going to actually get results from our questions.

Lynn Hull:
Yeah. So, I'd recommend, I think, people often come either two ways. They come in with—to tell us things and then this listening session, or they sometimes will give us almost the entire application, ask our opinions about it. And that's a review question, right? But if you do have specific questions about the study design or something you're thinking about doing, whether or not we have suggestions for that before you do it, I think that's when you get the kind of most fulsome kind of discussion and input from us.

And we are—you know, have been moving towards having more, you know, in-person discussions as response, you know, for meeting requests versus for a while—especially with COVID, it was a lot of just written responses because the limitations we had for anything in person. So, it has opened up a little bit more since then. But yeah, I would definitely package like what you're sending us with your actual thing that we can help you with, like a question for us versus is it good like will this pass muster? Like those kind of questions are review issues. But yeah, and then if you have questions, for example, about any modeling type of thing, like that would be a great place to bring it to us and discuss it with us in that avenue.

And then I just wanted to—if you want to talk about the behavior, I think that maybe it's a little misunderstanding, but the inexperienced, experienced, you want to talk about that? You can. We all can.

Carolina Ramoa:
I'll talk a little bit about the experienced user experience component. What I was intending there was if a study is done and the user population is completely inexperienced with an ENDS, the PK curves that I will see, the nicotine exposure will be lower than after they gain experience. So, my abuse liability assessment of that will be incorrect. So, I really look for the inclusion and the exclusion criteria of the population to make certain that my abuse liability assessment is correct for the likely and intended user population. So, I'll look at both of those.

So, you see a progression in a change of puff topography and that's—that leads to a change in nicotine exposure as well. So, it's just a study quality component that we always have to evaluate and look out for.

Willie McKinney:
I'm confused as to why you suggest that your interpretation of the data would be incorrect. Because in the marketplace, people use these products. They become familiar with them and in essence, that's where they settle. So, recruiting people that have a familiarity with the products gives you actually, an accurate measure of what's happening in the marketplace. So, did I misunderstand? And also, do you guys have guidance on your weight of evidence in terms of there's the nicotine, the rate, and the level, and then there's these use parameters, like which one do you pay attention to and why?

Megan Schroeder:
Regarding the first comment on the experienced user population, we absolutely agree that we want to understand what the abuse liability of these products looks like in the people who are using them, the likely user populations, dual users in most cases of ENDS and cigarettes. And so, like Carolina articulated, having really robust and well defined inclusion and exclusion criteria would only benefit your case. And it's an advantage from the reviewer's perspective because we know exactly what we're looking for. There's a ton of different types of users out there. We recognize that as well. But to the extent that your applications are able to hone in on one of those likely user population populations or those intended user populations and focus your data on those is extremely beneficial for us. What was the second question?

Lynn Hull:
Yeah. Willie, what was your second question?

Megan Schroeder:
Yeah. You had a second question, I know. Sorry.

Willie McKinney:
I just—more like a weight of evidence.

Megan Schroeder:
Oh, weight of evidence. Yeah. I will say that I wish we had something like that. But you know, abuse liability is really complex. And Carolina articulated really well the intersection of qualitative and quantitative data. And with such a multifaceted dimensional product characteristic as abuse liability, we don't have that. We have to consider each piece of evidence together and that's what we use.

Ed Carmines:
So, do you have a definition of what an experienced user is? A smoker is someone who's smoked a hundred cigarettes in their lifetime. So, is an experienced vaper someone who's vaped a hundred times?

Carolina Ramoa:
That's a spectacular question. It's a really hard one to specifically define. It's going to come down to each individual case. We're going to look for your justification of it. We're going to look for your inclusion and exclusion criteria. Literature also talks about it a fair amount. So, there—it

would take a justification. I don't have a specific answer for you. It would depend on the person, on the product. And when I say the person, I mean the population. Yeah.

Ed Carmines:
So, you also mentioned, I think when you talked about the quality, it was the number of subjects. You can't really power these studies.

Carolina Ramoa:
How so?

Ed Carmines:
Well, if you're powering to show a difference from cigarettes and say you're going to do the liking, I mean, you know, the—all of these products are going to be liked less than a cigarette. They're going to—their ability to reduce the urge to smoke is going to be less. You know, I've never seen an ENDS that was better than a cigarette that cigarette smokers would say, "Yeah. I'm going to do that and not smoke." It's always less.

So, you can't—there's no way to really power that to show a significant difference in those numbers. If you're looking at like the Emax effect or something like that, you know, that it just doesn't happen. You can't—you'd need such a large number of subjects to show a statistical difference in liking or urge to smoke that it's not possible to run the study. You know, you're at 50, 60 subjects, something like that.

Megan Schroeder:
Powering to more subjective effects is definitely a difficult hurdle to overcome. And you may be able to power your study based on more pharmacological quantitative measures.

Ed Carmines:
Yeah. But even powering on nicotine. So, if we're looking at Cmax, I mean it used to be that ENDS didn't perform. Now the ENDS are right there with cigarettes. They're just as fast. Tmax is the same. Cmax is equivalent. So, you're basically getting the same or maybe even higher levels of nicotine in some of these products than you would get out of a cigarette.

Carolina Ramoa:
I would—I'm going to repeat myself and I'm sorry. But I would absolutely include a justification depending on which outcome measures you have in your study. And I mean this is a very nuanced question. I think it goes beyond this panel. That's absolutely a meeting request question. I think it's a fair meeting request question. And I did want to highlight the difference—again, the difference between the listening sessions and the meeting request requests. Like if you want to be—we will always listen. You can always ask for those. But the meeting request is where you actually get an interaction.

And to repeat what Lynn said too very aptly, if you ask a yes or no, that's a scientific review question. It's going to be very hard to answer. If you ask too broad of a question, then it's hard to know what you are looking for. So, in terms of powering a study, we will look for your justification. We will look for what your outcome measures are, how many you have, and why

you did what you did. And we can also discuss that at a meeting request.

Lynn Hull:
So, I've been told. I know we're doing a great job talking to each other, but to talk into our microphones a little bit closer to make it a little louder. And real quick, I think I remember Willie's—you had a question about, I think, the—how to design the study. So, if you're talking about prescribed use versus like what—how to make sure you're using a correct prescribed use protocol, then again we would say to justify it to us about why you chose that prescribed use. And if you look back at the slides from Carolina, she had examples of both the prescribed use and then the ad libitum section and that can help get that as well. Okay.

Ed Carmines:
So, how long is—

Lynn Hull:
Oh, I'm sorry. I'm just going to—we had a question just a minute ago. We'll come back to you. Go ahead.

Steven Haddad:
So, we've talked about these qualitative and quantitative factors within the PK studies. My question is more on the inner workings of FDA. So—or this decision-making process. So, on the quantitative side, it's more objective. The analyst probably has, you know, a set of ranges that we should hit. And on the qualitative side, it's more subjective.

My question is how is it working with you guys deciding these applications and reviewing these studies? Is it one person looking at a study for a particular application and then another person looking at a study for a different application, or are you guys looking at them as a group? Because this is what scares us as the manufacturers and the applicants, right. We've spent a few million dollars on our studies. And we submit. Certain things are subjective. We get the wrong analyst that thinks a certain way. They say, "Oh, this doesn't work. It's not APPH. We don't like it. MDO." Versus another analyst that looks at something and says, "Oh, this makes sense." Right? My question is how is that working? Is it a group effort looking and making these decisions or is it like, when I call Delta and somebody tells me no and I hang up and I call back and then they give me the credit?

Lynn Hull:
Well, it's not like Delta.

Steven Haddad:
Yes. [laughs]

Megan Schroeder:
So, this is a government.

Steven Haddad:
No, no.

Megan Schroeder:
There is no point person making a decision. These—all of these abuse liability evaluations are going through extensive, extensive, extensive reevaluation, secondary review, tertiary review. Nothing—no decision in CTP and Office of Science within my branch in behavioral and clinical pharmacology is made by one person. It's all—we're making decisions in the context of what we know about the class of products so that we can make consistent decisions.

Steven Haddad:
Great. Thank you.

Lynn Hull:
And similar to that, like the overall application has—you know, all the different disciplines have their reviewer or review team that goes to the same levels of checks and balances. And then it's all speeds into an overarching decision looking at all the different factors. So, it is really a large group that—and we make an effort to be consistent between applications working, you know, beforehand and how we're going to think about looking at things as we go along, as we learn things. So, it is an iterative process.

Carolina Ramoa:
To decrease your anxiety further, I've been at the government for 10 years now. I run a team. Megan's actually my boss. And I have never experienced so many levels of clearances and discussions the way it's iterative. There's no one disgruntled person that will take things off track. That's—I don't—it's not possible in my team. It's not possible on her team. We really—I mean, I don't know how to say this other than we want good data. Make my job fun. Let's go. Like, let's look at this. And I'll look at it with my staff. I'll look at it with Megan. Megan will look at it with her—we'll just keep going. There's no one person.

Also, the team is multidisciplinary, right? We got engineers on here. We got chemists on here. We got social scientists. We really get to debate these scientific concepts that we find very interesting and apply them to public health, which is what really excites us. So, there's a lot of discussion that happens in a really nuanced way. And we are looking and really, really reading what you're sending us.

Willie McKinney:
One of the challenges small manufacturers have is we—they would like to have more meetings with the FDA. And I know you mentioned some very specific meetings, but there's limitations. If you go into scientific review, if you get a deficiency letter, "By the way, the learnings here have been great. Can I go back and amend my application?" Well, it depends on where it is in the process. But you're going to look at my application according to what you just told us today. So, it's a challenge for us to have that meetings.

And I'll just be specific here. When you sell e-cigarettes to a correctional facility and you're asked to do a PK study, well, that's a vulnerable population. And you got to be creative and think of a way to—if you feel you need to do it and if they feel you need to do it—to get that data. It would be nice to be able to discuss that approach before giving it to you. And I almost said

something I shouldn't have said—and you say, "Well, that's not appropriate," right? So, how do we have more meetings, regardless of where our application is in the process, to understand what you're currently thinking?

Megan Schroeder:
I will say, you know, this is one example, you know, we're putting out memos and things like that. But I don't think these kind of broad discussions are getting to what you're asking. You want very product-specific, application-specific information. And meeting requests are the best way to do that. FDA wants to provide you with the best sound evidence and the best suggestions and recommendations because we want your data to be great so that we can look at great data and make an evaluation.

So, we do have the same scientific goal at heart here. And I think we can have these great conversations in smaller group meetings so that we can focus on individual applications. And you know, speaking with your—about your vulnerable population, absolutely make that argument in an application. Use the literature to the extent that you can. I think all of these are, you know, we're all about being creative.

And I think that's kind of the dialogue here is how can we be creative in the requirements that FDA has to efficiently and scientifically look at these tobacco products under the APPH standard. And it's—we're needing to be creative in how we work with small business. And I think that the best way to do that is in a meeting about—where we can specifically talk about the specific situations associated with your company.

Lynn Hull:
And we are making a push to have more ongoing conversation, particularly during the scientific review, with applicants. We've been kind of started that in the fall and that's something that has proven very valuable and ongoing as we move forward.

Willie McKinney:
So, that's happening—that's going—I'm sorry I missed it. So, that's a new process or something new?

Lynn Hull:
Just having more conversations with applicants, particularly about things that either we aren't able to find in an application or we feel are in data that they likely have that they can share with us versus going straight all the way to a deficiency letter to find things that they have. Like, so it's often—not to go outside of our panel, but often it's a little bit more like product characteristic information type of things. But, generally, yeah, we've increased our dialogue with the applicants.

Char Owen:
Is that—in what stage of the process is that? Is that before a rejection? Because normally in small business, we don't hear from anybody until we get the rejection or we get into scientific review. There's nothing in the middle.

Lynn Hull:
Right.

Char Owen:
So, is that a new process that's going to be something in the middle for us?

Lynn Hull:
Yeah. I'm talking about scientific reviews specifically.

Char Owen:
Specifically, only scientific.

Eric Heyer:
Not being specific about a particular application or particular product, but can you just define what the goal is or what the standard is that you want applications to meet that's going to be kind of check that box. If we're looking at overall APPH, abuse liability is one of the boxes to check. What is going to be sufficient? Can you define that for us just, I mean, as an industry?

Lynn Hull:
I mean, I think Carolina's discussion about the kind of different criteria that go into a PK study and the other types of study design captures that. But you can talk about that a little bit more.

Eric Heyer:
What do you want to ideally see to say we like the abuse liability profile of this product? Can you define that for us?

Carolina Ramoa:
No. [laughs] I mean, I can't define that for you. It is a product-specific evaluation based on each outcome measure. It's going to be unique to each intended and likely user population. And as we talked about the combination of these many, many, many variables are infinite. So, to set, like, this amount of nicotine exposure in the blood is not feasible but what—I mean, I don't think—I'm not sure if I'm answering right—if I answered your question completely.

Eric Heyer:
Well, you understand the problem and the dilemma this poses for small businesses that have limited resources. It's like, if there's—it's not a moving target, it is no target at all, right? I know—

Megan Schroeder:
You articulated the whole Goldilocks principle earlier.

Eric Heyer:
Right. Because I mean—and I've seen plenty of TPL reviews, I've seen plenty of reviews out of—you know. And it seems like it—sometimes it could—and again, I'm not to get on a soapbox, but it seems like it sort of depends on what the reviewer had for breakfast that day. It's like, well, it could be too much or it could be too little and there's no set standard or set goal.

And we need objectivity. This industry needs objectivity.

These are—I mean, these are multimillion-dollar studies you're asking people to do and you have no idea what you're shooting for going in. And this is part of this segment of the industry's massive frustration with the agency. Apart from again, why are we even doing these to begin with? Because they don't speak to harm reduction or morbidity and mortality. I think if it were up to me, just get rid of them altogether. They're not necessary for this class of products.

Lynn Hull:
I mean, I think they'll talk a little bit more in our later section about toxicology that these are not risk-free products. Okay. And having a product out there which does increase abuse liability that's not documented in any way and we aren't aware of. I'm not sure how you'd expect us to make a decision if that's appropriate for public health. So, we do need to know where they fall in the continuum of abuse liability. So, we can evaluate overall as part of that, where they fall in continuum of risk and products.

Carolina Ramoa:
And I'll also add to that that addiction is a health effect. So, that does contribute to morbidity and mortality in that.

Eric Heyer:
Right. But nicotine as such, isolated from the other things that come along with the delivery vehicle is, you know, the physiological threats that that poses are minimal compared to all the other things that come along with, for example, combustible cigarettes. So, this is—you know. And so, anyway, I won't go on about it. I think I've kind of made my point today.

Willie McKinney:
To build upon a little bit of what Eric said, you know, it appears that there's sometimes some unwritten standards where you do a PK study and your Cmax is similar to—almost identical—to a cigarette. You do the ad lib, you know, similar to maybe slightly higher than a cigarette, which some people have argued you have to pull people away from cigarettes. So, there needs to be some abuse liability. But you've crossed that threshold. So, you're done. Your product, go change it, do whatever. That's a standard, but it's not written. But everybody kind of knows it. At least I think they do anyway. Can you guys comment on that?

Megan Schroeder:
Regarding if you've got nicotine exposure in an ad lib portion of your study that's going higher than a cigarette, for example, explain why that's not going to pose an additional health risk via abuse liability and addiction to us. Help us understand why that would not raise a concern from our behavioral and clinical pharmacology perspective. But again, we're not the ones making the decisions. Our abuse liability decision is just one piece of this. We're looking at the switching behavior. We're looking at the toxicology associated with that switching behavior. We're looking at the manufacturing and all that kind of stuff. All of that goes into the decision-making. And the abuse liability piece itself is not sufficient to make a determination overall.

Char Owen:

So, you brought up a good point about that, about everything being—about all those things look like to me how it makes them feel or whatever, or the switching behavior that's in adult studies or whatever. To me, this PK is all about how does the nicotine perform in the body, right? How's my product—and I agree with that, I need to know how my product—how nicotine is reacting inside the human body.

But with small business and with my own company, the PMTA process has felt really undefined. Where we have a goal of APPH but we don't have a clear structure for it to be defined. Would the FDA be opposed to defining a model that would help us better filter out our own deficiencies? So, a model for APPH before the application is refused or even really filed. So, you know, scaling perhaps, you know. And in other words, something that we can utilize to say, "All right. I may be a little short here, but I'm knocking this out of the park. And so I get extra credit for this work." We really have no structured model for APPH at this point, and it feels a little undefined.

Lynn Hull:
I appreciate that concern. I do want to focus back to the pharmacokinetic aspect just because that's the topic of our conversation.

Char Owen:
Yeah. Okay.

Lynn Hull:
But it is a piece of that for sure.

Char Owen:
Yeah.

Willie McKinney:
I'd like to ask the question that was asked me about explaining how that PK data would not cause a problem. And honestly, I don't want to have to explain it. So, I would advise my clients to make sure that their products don't exceed that of cigarette. But I've drawn a line and I—in essence, I've sensed that FDA has a line because it would be very difficult to explain to you. I'm just looking at you, I just know it would. So—

Megan Schroeder:
I am very friendly.

[laughter]

Ed Carmines:
So, you mentioned the ad lib and so we do the controlled use, force puffing, certain time scale, we collect blood and do plasma analysis. What's your ideal ad lib time duration?

Carolina Ramoa:
It's another wonderful question. So, the longer we know how people use these products, the

longer we have use behavior—chronic studies, for example—the more we know, right? The more information that we have and the faster that we can make an abuse liability determination. So, I would—you know, on a practical level, I would suggest looking into literature to find that. I can't give you an exact time again because I don't want to be held to a standard because that's not the goal of today. But I would look into literature to look at ad lib and I would really like to know long-term use behavior. Chronic nicotine exposure is very interesting and very useful data as well.

Ed Carmines:
So, there's a limit on how much blood you can take out of people? No. I mean there is recommendations and you can't bleed them forever. So, that becomes a limit on—and there's also a physical limit for the laboratories if they're going to try to do the controlled and the ad lib in one day.

Lynn Hull:
So, was your question about how long the ad lib session should be, or how long the collection of the sample should be?

Ed Carmines:
No. How long the ad lib should be? What's the ideal length? And so, there are physical problems.

Megan Schroeder:
Well, typically in ad lib situations and scenarios, you're not—you're doing sparser sampling or you can do urine collection or something like that. So, you're not bleeding the patients to death.

Ed Carmines:
You're not bleeding them continuously.

Lynn Hull:
We don't recommend that, no.

Megan Schroeder:
Right. No one wants that.

Ed Carmines:
You mentioned, you know, this chronic abuse liability and I hadn't really thought about that. So, would you accept a chronic study with total nicotine equivalence without doing an abuse liability? So, you can demonstrate that the total nicotine equivalence is the same after, say, a weeks of use?

Megan Schroeder:
I think we also—I think that's an—we would love that data, just saying that. But we also need to understand the pharmacokinetics of the product. That really shows the extent to which that product is addictive and how the nicotine is absorbed and how quickly that is being absorbed. It could be a situation where you could use those data to help bridge two pharmacokinetic studies. Again, we're trying to be creative here and using bits and pieces of data to help fill in the abuse

liability puzzle. And I think that's a—

Ed Carmines:
Total nicotine equivalence for 5 days would be much cheaper than—and quicker than—a abuse liability study.

Lynn Hull:
And we're also looking at different populations. We're looking at people who are current users or people who are using tobacco products and expect to switch. But we also have a duty to think about people who are nonusers. And so how existing users use it chronically is a really important piece of information. But the information about how quickly something's absorbed the Tmax that can inform us about somebody who's using it for the first time or is inexperienced altogether.

Willie McKinney:
One of the terms we've heard quite a bit is standards. And I got a feeling we're not necessarily communicating right now when we talk about standards. When I think about small manufacturers, it is—and I'll build off what you said, Steven. If I'm going to spend the money and do this study, give me an idea of an outcome that's just going to kill my application, right. Where is that line? You don't have to tell me, this is good, this is bad, but where is that—you know, if your PK study shows that there's greater abuse potential than a cigarette, that's going to be a challenge. Just that communication is enough to provide guidance to these guys.

Now, I would come back and say, "Why do I need to do a PK study and try to make that argument?" That said, also, if I make that argument, am I going to get a refuse to file? Which I would argue that that argument should go to scientific review and be debated, not a refuse to file because I filled something in. You guys want to comment? Am I correct about the communication you want?

Megan Schroeder:
I think standards are tricky when you're talking about individual discipline—like a standard that an individual discipline holds when we're talking about an APPH assessment that really looks at all sorts of—it's a multidisciplinary decision. And so, a product standard—we wouldn't call it a product standard because it's not for the global decision-making. But a guidance or a quote-unquote threshold for one discipline, particularly one that deals with behavior is really tricky. And we don't have that.

Willie McKinney:
But it's a relative assessment, right? I mean we're moving people away from the most harmful tobacco product. So, it's relative.

Eric Heyer:
Yeah. If I can just chime in there. I mean, going back to the point I think that you made, Lynn, is if, you know, if I have—there was some discussion today about—well, there's some of these products that almost have HPHCs that are at the levels of combustible cigarettes. Well, obviously if I have a product that has that profile—this is going to be a much more important question. If all my HPHCs are—or, you know, tox results are looking very strong and minimal compared to a

combustible cigarette, then why is this so important, right? Why does it really matter in terms of morbidity and mortality?

So, yes, one—you know, you have—there's this push and pull of the different elements of the APPH evaluation. But it seems like there could be some lines at least drawn to help people to figure, should I spend another few million dollars doing all these other studies on the application or if my PK study is, you know, past that threshold, it's going out anyway? So, you know, that shouldn't be that hard to engage in that one line-drawing exercise.

Lynn Hull:
And I don't think it would be a surprise to you guys that these are—this is a really variable product category. I mean even amongst people we've talked to today, you guys either you have some have devices only, some have open e-liquids, some have closed systems, some are disposable. There's a whole lot of different varieties and they all kind of have unique challenges. And so, again, like, we don't like the word standard because tobacco product standards are a regulatory thing that we can do, but that takes a huge burden of evidence to move forward in a lot of different pieces. But even offering, you know, [unintelligible] guidance is another name for a document, but informal guidance like us talking about in meetings that we've had about different things we'd take into consideration. It's—for us to make an across the board, this is the thing. I don't know that that people would be altogether happy either because their products are so different. And so, what—you know, at this point, I don't think it's—we're ready for that to make those kind of determinations. If we were, maybe it would be a product standard that we would apply. So, it is, I think part of the ongoing conversation about the different things that we take in consideration. Things that we've recommended would be helpful to think about in the study design to help us understand the products. But I—even though I keep hearing, I think, that you guys would love for us to tell you what to do, I think that if we did, you might not like it as much because then it look like, you know, you would like to have a little bit more flexibility—sorry, I'm far away from microphone. A little bit more flexibility and, you know, making the case for your product and justifying, you know, why you believe it's APPH for us to, you know, evaluate.

Eric Heyer:
Well, thus far we're batting 0 for however many millions. So, I mean, you know, that's again, the frustration of the industry. But yeah.

Char Owen:
So, earlier in my first question, I asked if you guys were actually looking into the new sciences such as PBPK modeling and stuff. And if you are, is there a way for us to access that information? Is that something that we have—we can have either a dialogue or access to?

Lynn Hull:
We don't have a model like that to share with you guys. If you guys have a model that you're thinking about or interested in and want to come and discuss it with us, we'd be happy to have that conversation.

Ed Carmines:

So, how good would the PBPK model have to be, 20 percent, 5 percent? What do you want?

Char Owen:
In the [unintelligible], I believe it's 35 percent, but standards are usually 20 percent. So, there's a memo from Dr. Holman on that in 2024 and 2016, isn't that right? I believe it's 2024. It's about the SE pathway, but it does talk about those.

Lynn Hull:
Right. And SE pathway is different. I think we talked a little bit in the earlier sessions about the differences.

Char Owen:
The [unintelligible] margins are outlined in that.

Lynn Hull:
Yeah. But that is a one-to-one comparison between an existing product and a product that's been kind of moving the bar a little bit or being further developed, which is a very different consideration than a PMTA, which is looking at a new product against the existing marketplace.

And I think we're at the end of our time, I understand from the time. Am I right? Just 3 minutes. We got 3 minutes. So, last round, you guys, with the last question?

Ed Carmines:
So, when you talk about your theoretical study, you talk about visits. Do you have a preference for inpatient versus outpatient studies?

Carolina Ramoa:
The study design will dictate the preference. Which one makes more sense with the design that you create? So, I think this is a question that kind of highlights everything. All these decisions have to be made within the context of the specifics of the study design, specifics of the product. And so, it's really—that's why it's so hard to tell you yes or no or to give you a specific number. In study, inpatient design is great for certain outcome measures. And lab visits and out of outpatient study is better for other outcome measures.

So, my next question within a meeting request context, for example, [laughs] would potentially be what outcome measures are you looking for? And then I can better help determine which design correlates with the outcome measure. If you're coming with specific questions, I'm sure that we could discuss that kind of thing within the context of a meeting request.

Ed Carmines:
So, you know, for most of the small manufacturers, they didn't design their products to pass the PMTA. They designed their products for consumers. And you know, they didn't—we're not considering abuse liability or HPHCs or anything. There was no real design element to these products. They made something that worked that they could sell. And so, now most of them are backfilling. So, they're running studies to demonstrate that their products are appropriate for the protection of public health, but at a risk of, you know, they don't know, you know. Luckily,

HPHCs are down, don't see any tox, you know. The nicotine PK is about the same. So—and you know, switching data, if they have switching data, says that people are going to use these products to quit. I mean that's, you know, where we get to the bottom line here. But nobody is really designing products to do that.

Willie McKinney:
Ed, are you referring to early applications and early applications that are still in the system and the process to amend those? You may be correct about early applications, but I think most people have gotten a little wiser now.

Ed Carmines:
Well, I don't think that people are running PK studies to help them design the product. The PK is at the end of the process.

Willie McKinney:
No. They're using aerosol chemistry and pilot studies.

Ed Carmines:
Yes, which is the aerosol collective mass. And you can look at the aerosol collective mass and figure out what's going on in the nicotine. That gives you a really good idea. And then the pH and maybe, you know, whether it's freebase nicotine or not. We haven't talked about salts. No one mentioned salts versus freebase nicotine and what your thoughts are there.

Lynn Hull:
Unfortunately, I think—

Carolina Ramoa:
I mentioned it in one of those—in the product characteristics slide showing that there's nicotine formulation that can change nicotine exposure. So, in that context, we mentioned it.

Lynn Hull:
So, on that note, I'm going to say thank you so much, you guys. It's a great conversation. It's been really nice to hear from you. And our next panel is the Panel 4, Studies of Adult Benefit.

[side conversation]

Benjamin Apelberg:
Great. Okay. Is this working? Great. Hi everyone. Good afternoon. My name is Ben Apelberg. I'm the Deputy Director for Regulatory Science in the Office of Science. I'm really pleased to be here to moderate what I'm sure will be an interesting and fruitful discussion in the Studies of Adult Benefit panel.

So, in this panel we're going to be talking about the design and conduct of studies designed to assess the effectiveness of an ENDS product in helping adult smokers switch away from combustible cigarettes, switching completely or significantly reducing their cigarette consumption. You know, as you can imagine, understanding the extent to which particular

ENDS products can help transition smokers away from combustible cigarettes is, you know, is really a critical aspect of the evaluation of these products along with obviously some of the other topics that were discussed today.

So, just to give you a sense of how the session is going to go, we're first going to start with a presentation from FDA to kind of level set, provide some context for what we hope will be a great discussion. Just as a reminder, I'd really like to keep the discussion focused on the science. And we're really interested in hearing from the panelists in terms of their experiences, their perspectives on the planning and conduct of these types of studies. I want to remind folks, Todd mentioned this earlier that there is a docket that's open and will remain open. So, if there are topics that we don't get to today or, you know, additional things you want to comment on, there's that opportunity as well.

So, without further ado, I'd like to introduce our FDA speakers for this panel discussion. We've got two speakers. Dr. Mollie Miller will start. She's a senior health scientist in the Division of Individual Health Science at CTP. And then she'll be followed up by Dr. Amy Gross, who's an epidemiologist in the Division of Population Health Science. So, I'll turn it over to you guys.

Mollie Miller:
Thanks, Ben. So, as Ben mentioned, my name is Dr. Mollie Miller and I'm a health scientist in the Division of Individual Health Sciences at CTP. Today, along with my co-presenter, Dr. Amy Gross, we'll be discussing considerations related to the assessment of behavioral data to support an evaluation of adult benefits for flavored ENDS.

So, I'll start by reviewing some of the relevant background on PMTAs and the behavioral framework that CTP uses to evaluate the risks and benefits of flavored ENDS. Next, I'll discuss the different types of studies that can be used to evaluate potential adult benefit, including clinical trials, cohort studies, and actual use studies.

The APPH standard is the regulatory standard for the PMTA pathway, and FDA is responsible for making that assessment during product review. The APPH standard is a whole population standard, meaning that our reviews consider the risks and benefits to likely users and nonusers of a new product, whether people who are currently using other tobacco products would stop using those products or switch to the new products, and if nonusers would start using the new products. The evaluation of behavioral evidence of adult benefit is only one aspect of PMTA review, that along with findings from other review disciplines, is integrated by the technical project lead and overall APPH decision-making.

Preventing youth use is a key consideration in product review because almost all tobacco initiation occurs before age 25. And in the case of ENDS, there are still many unknowns about the long-term health risks. With regard to non-tobacco-flavored ENDS specifically, FDA has previously communicated that there is a known and significant risk of youth appeal, uptake, and use. This risk is well documented in the scientific literature.

For example, findings from the 2024 National Youth Tobacco Survey found that nearly 90 percent of youth currently using ENDS reported using a flavored product. Additional research

has also shown that flavored ENDS facilitate initiation and ultimately promote transition to regular use. Regarding the potential for adult benefit of ENDS, while no ENDS products have been approved by CDER as a smoking cessation therapy, a growing body of evidence suggests that ENDS may facilitate transitions from cigarettes.

For example, a 2025 Cochrane Review concluded that there is high certainty evidence that electronic cigarettes containing nicotine increase smoking cessation rates compared to nicotine replacement therapy. Although it's also important to note that ENDS vary widely, which may influence their ability to aid in switching and cessation. For flavored ENDS in specific, although flavors are known to be appealing to and widely used by adult smokers, there's limited data and mixed findings about the benefits of flavored ENDS as a category for switching and cessation.

So, in reviewing PMTA's for flavored ENDS, FDA looks for robust and reliable product-specific evidence of a new product's benefits for adult smokers. Specifically, this means evidence that the flavored ENDS are likely to promote complete switching or significantly reduced cigarette smoking in adults beyond that of tobacco-flavored ENDS. The need for this evidence of added benefit is specifically due to the known risks of flavored ENDS for children and young adults under age 21. By contrast, tobacco-flavored ENDS are associated with a lower risk of youth use and appeal. Therefore, the strength of evidence and the magnitude of benefits to adult smokers that's needed in the application is relatively lower and may be derived from other data sources.

Based on our experience reviewing PMTAs and of the scientific literature, FDA has determined that the two types of evidence most likely to demonstrate this added benefit include experimental evidence from randomized controlled trials, as well as observational evidence from cohort studies or actual use studies. The FDA would also consider other evidence that reliably and robustly evaluated the impact of the new flavored versus tobacco-flavored ENDS on switching or significant cigarette reduction over time among adults who smoke cigarettes.

When present, such information is evaluated to determine if the potential benefits outweigh the significant known risk to youth, such that marketing the new flavored product would be APPH. So, now I'll turn the presentation over to Dr. Gross who will discuss these study designs in more detail.

Amy Ross:
Thank you, Dr. Miller, for handing this over. So, one approach applicants may choose to take to demonstrate adult benefit of a new flavored ENDS product is to conduct a randomized controlled trial, or RCT, using the new flavored ENDS. In the context of tobacco product applications, an RCT is a study in which participants from a target population are assigned randomly or with equal chance to experimental conditions. Resources such as the CDER guidance on developing NRT or published literature on best practices in smoking cessation trials, while intended to assist in the development of cessation therapies, may be useful to applicants when designing a trial to demonstrate adult benefit of flavored ENDS.

This diagram provides an illustration of a possible RCT design. Participants are recruited from a desired study population, such as current combusted cigarette smokers, and randomly assigned to a study condition such as using a flavored ENDS or a tobacco-flavored ENDS. Throughout the

study, outcome measures such as combusted cigarette use can be collected and compared between groups.

With the appropriate sample size, randomization of participants in RCTs minimizes confounding and the potential for preferential assignment, and studies. Analyses typically allow for causal inference about the impact of switching to a new product. In this case the added benefits of a flavored ENDS over a tobacco-flavored ENDS comparison on the outcome of cigarette smoking abstinence. These conclusions can inform FDA's assessment of added benefits for new flavored ENDS.

The study design employed in an RCT may vary across applications according to the number and variety of products included, but the study should be prospectively designed and statistically powered to evaluate changes in primary outcome measures. For flavored ENDS applications, FDA looks for participants to be randomized to use the tobacco-flavored ENDS or the flavored ENDS. In applications with multiple flavored ENDS products, product-specific information will be most valuable when participants are randomized to use a particular flavored product.

An alternate study design may include randomization to a general flavored product arm where participants could choose their preferred flavor out of the flavored new products available. However, this latter study design may be more difficult to discern what role an individual flavor may have on switching or reduction in use.

Ultimately, FDA looks for the applicant to justify the approach taken to analyze data from a combined flavored product condition and how the analysis can support FDA's product-specific evaluation of each flavor. FDA also considers observational studies to provide the required robust and reliable data for flavored ENDS. In many settings of observational studies, good study design can be guided by outlining the idealized RCT that you would like to conduct and then designing both a study and analytic approach to best approximate that RCT.

Just like in an RCT, the cohort study samples and enrolls participants from the source population of interest, but without the many benefits of randomization. FDA reviews baseline data collection, including detailed demographics and tobacco use assessments in order to address potential confounding. Additionally, tobacco product use in a cohort study is determined solely by the participant and can vary over the time period. Therefore, accurate assessments of all tobacco products used across the entire study period are critical.

In a cohort study, participants typically do not receive additional guidance or coaching on their tobacco use behavior. Those behaviors will often be very dynamic compared to RCTs. People using ENDS may try different flavors of a product, rotate between one or more flavors for more usual use, and so forth. Follow-up assessments throughout the length of the study should accurately assess these changes in use of flavored products over time. Current established smokers in particular may also use other tobacco products in their efforts to reduce smoking, switch, or quit, and may also use approved cessation therapies such as NRT or non-NRT medications.

Use of any of these products should also be assessed as they may be potential confounders, and

stratified or adjusted analyses may be necessary for unbiased estimates of the main effects of flavored ENDS products. Evaluation of the tobacco-flavored comparison product in the same study as the flavored ENDS product enables the most valid comparisons. FDA does not recommend a specific length of studies in determining added benefits of flavored ENDS. FDA looks for the study duration to be appropriate for the outcomes being investigated and scientifically justified.

In studies evaluating adult benefit of flavored ENDS, outcomes of interest such as combusted cigarette abstinence often occur gradually over time. Thus, the studies will likely need to evaluate behavior over an extended period. Published literature has recommended 6 months as a standard follow-up duration for assessing differences in smoking abstinence between experimental conditions, allowing for an evaluation of lasting behavior change. However, FDA also acknowledges a study less than 6 months long may also inform an assessment of the added benefits of a flavored ENDS product. Whatever study duration is chosen, FDA reviews for scientific justification in the study protocol.

Moreover, given that short-term abstinence is unlikely to confer health benefits and is often associated with relapse, studies with follow-up periods shorter than 4 weeks may not be sufficient to provide robust evidence of behavior change. A significant issue in long-term studies is the potential for loss to follow-up, and FDA evaluates the various approaches that may be used to handle this limitation. Complete switching and significant reductions in smoking are the most typical outcomes of interest in studies to evaluate adult benefit of flavored ENDS. Complete switching is typically defined using past 7-day or past 30-day abstinence. Longer studies of 6 months or more duration might also consider a maximum allowable number of cigarettes.

Additionally, applicants might also pool complete switching and complete cessation of all tobacco into a secondary endpoint of total smoking cessation. In our experience, applications that assess complete switching are generally more successful. However, significant CPD reduction may also be assessed. CPD may be reported as both a binary and a continuous outcome. When reported as a binary outcome, FDA suggests justifying the threshold value used in the application narrative with supporting literature.

In addition to cohort studies, another type of observational study is the actual use study. Actual use studies differ from cohort studies mainly in terms of how the products are obtained. In cases where the new products are not currently on the market, actual use studies may be the most appropriate option versus a cohort study.

While product-specific information permits the most rigorous evaluation of adult benefit, in some cases, evidence on each individual flavor option or nicotine concentration may not be feasible. Bridging data from one of the applicant’s flavors to another flavor may be appropriate. FDA's bridging evaluation focuses on whether and to what extent differences between new and bridged study products may affect outcomes related to adult switching. Applicants should consider how the various flavors and flavor constituents in the new products may impact use behavior and may differentially influence switch rates compared to the bridged product. Applicants should provide data and explicit justification to support this bridging, such as abuse liability data.

Thank you for your attention and interest today. So, we'll now pivot to our panel discussion. And Dr. Miller and I will be accompanied by Dr. David Portnoy, the Acting Director of the Division of Population Health Science, and Dr. Sarah Johnson, senior science advisor in the Office of Science.

Benjamin Apelberg:
Great. Thanks so much, Mollie and Amy. So, you already did the introduction for our FDA panelists, so I'll just turn it over to our panelists who are representing small businesses. And I'll just ask you to introduce yourself what company you're representing and kind of, you know, any initial remarks related to your experience on the topic or other things you want to share.

Dino Baccari:
Sure. Good afternoon. Yes, I'm—

Ryan Muckenthaler:
I'm Ryan Muckenthaler and I'm a member of Lotus Vaping Technologies. We are a small business manufacturer. We manufacture American-made e-liquid. We began operations in 2012, and we employ around 275 professionals that support our manufacturing, distribution, retail compliance, operations. Specific to this panel though we were—with some help from some of the other panelists up here, we put forth the first-of-its-kind study with the longitudinal cohort study in 2023 on that one. So, I'm really excited to talk to FDA about that today.

Eric Heyer:
I'll introduce myself again. My name is Eric Heyer. I'm a partner in the Washington, D.C., office of Thompson Hine. I'm a lawyer. I'm here today on behalf of Maduro Distributors that has pending PMTAs—high-quality PMTAs for their Loon branded disposable ENDS products. And I guess we'll do introductions, and I'll come back to my first questions.

Jessica Zdinak:
Hello. I'm Dr. Jessica Zdinak. So, I am here representing on behalf of Glas. I'm also the founder and Chief Research Officer of ARAC. We're a behavioral science firms supporting many efforts along the regulatory environment. I have a phenomenal team and know many of you that are here today and really excited to be here and just to quickly note on behalf of Glas. So, for those that don't know, they're an innovative age-gated ENDS device, submitted application in July 2021, filed—FDA accepted and filed in December of 2021. And then went under scientific review in June of 2022, and then went into an expedited review queue under products with merit.

And I'll never forget the day that an individual from Chemular called me pretty quickly with a rapid request after an unprecedented second deficiency notice that they received in response to this specific topic, which is the importance of assessing the population-level benefit. And look forward to having the conversation of the results, the findings, and the current status. Yeah. So, thank you for having me.

Bill Wilkstrom:
Hello again, everyone. Bill, I'm the owner of two companies, Vaporized and Paradigm. I've been

in the industry since 2013 and continuing to look for ways to get a marketing order granted.

Benjamin Apleberg:
Great. And we've got a panelist on online as well.

Dino Baccari:
Hi. My name is Dino Baccari. Is that who you were looking for? And can you hear me?

Benjamin Apelberg:
Can we hear—can you try speaking a little bit louder?

Dino Baccari:
Hi. This is Dino Baccari from White Horse Vapor.

Benjamin Apelberg:
Okay. Great.

Dino Baccari:
Can you hear me okay?

Benjamin Apelberg:
Yeah. It's kind of low, but we'll work on the AV here. But thank you.

Dino Baccari:
Hi. My name is Dino Baccari from White Horse Vapor. Can you hear me okay?

Benjamin Apelberg:
Yeah. There must be some kind of technical difficulties, but we'll work on it. We hear you. Thank you.

Dino Baccari:
Okay, wonderful. So, I've been commercing in the vape industry since 2011, 2012, started as a—I was a smoker for a long time, and these products are the only products that ever helped me quit. And it just kickstarted this mission for myself to help others. And that's honest to goodness, the truth. What has always fueled my, you know, my path has always been, you know, I know and I don't think it's talked about or discussed enough, the most important part about vaping is the elimination of inhalation of smoke because that is the deadliest part of combustible cigarettes.

It's just proven over and over again, it's not nicotine, it's inhalation of smoke. If a building was to catch on fire and you didn't get burned, what would probably take you is inhalation of smoke. We all know that here. And other forms that have alternatives have come up in the past, have proven to be failures, 80, 90 percent range. And I was Politifacted back in 2017 in how great these products are. Penn State University even highlighted them as they're far less addictive than regular cigarettes. That's what's so incredible about them.

And I really pride, you know, the way we operate our business here at White Horse, you know,

because we're in the retail side of it, you know, to make really good decisions, you have to rely on data, especially when you're navigating through, you know, a large customer base. And you know, we're six figure, seven figure. There's so much accumulation from 2011, 2012 that we've learned so much from the transactions that we performed.

And you know, we have—it's not us just making this up. There's inputted data from our customers. I mean I can share this with you in which all of 90 percent of them have chosen flavored products like Nicorette. We know that, see, Nicorette gum is a great example how flavored products work and they attract a smoker, especially a smoker. Nine out of ten smokers want to quit smoking. Period, point blank.

And I mean, our average age, and this is all third-party verified that I be more than happy to share it with you. You know, we hover around 28 to 33. I mean these numbers for long data, big data, if you run this through any AI tool is going to give you amazing results and it debunks a lot of what we hear. And I was going to take this call from my office, but I jockeyed over here because I just wanted to give you—because we talked about visuals earlier, and I appreciate you asking for visuals. But I just want to give you an example of what a flavor ban or restricted access to these revolutionary products that have proven to save lives over and over again for adult, former adult smokers. This is what it looks like. There's nothing here, folks. There's nothing. There's nothing on the shelves. There's no more business. So, I understand how some of the participants feel that the urgency is mounting because the restrictions are mounting and this industry needs your help and we need it faster.

And I'm just going to finish with this. And lastly, you know, believe it or not, and this might sound corny as heck, but it's true. One of our core missions was to go out of business. That's really what it was and that's what kept us going. That's why we call ourselves White Horse is the light that shines through the darkness. Sounds corny, but it worked. And to us, going out of business is—there's never—nobody ever needs to smoke again. And if—

Benjamin Apelberg:
Okay. I appreciate the—

Dino Baccari:
No, it's just the truth.

Benjamin Apelberg:
No, no, I appreciate the comments but we're just at the intro.

Dino Baccari:
I know. I'm going to finish this. Classic menthol and classic regular, average is 49 since 2012.

Benjamin Apelberg:
Great. Got you.

Dino Baccari:
And they were taken down by the FDA.

Benjamin Apelberg:
Okay. Thanks, Dino. Appreciate it.

Dino Baccari:
Okay.

Benjamin Apelberg:
I just—so now I want to really turn it over to you all. If you have any additional initial remarks, feedback, you know, any things that you want to share to get this going.

Bill Wilkstrom:
Sure. If you don't—oh, go ahead.

Ryan Muckenthaler:
Dino makes a lot of really good points and, you know, he's absolutely right. When you look at a store like that that is dealing with such limited supply to service the customers that are requesting those flavors, needing those flavors, to continue their vaping experience, they're wanting to choose a product that is less harmful. And you know, I feel like the—before we really get started talking about some of the LCS studies, the public health principle, that non-combustible nicotine products are substantially less harmful feels like it's been displaced by a very youth-centric framing that has dominated a lot of the FDA's decisions around these products, despite continued declines in youth uptake. Interesting point with that though is that on recent surveys youth has on the top five brands are JUUL and Vuse which both have limited to only tobacco and menthol flavors. Those are two of the top five products that youth will get their hands on—have reported using. And I think it speaks a lot as to less about how flavors work with youth uptake and more the nicotine is going to be used. And I think that to frame this question appropriately, can the FDA change the narrative to stop scaring away adults? Does nicotine belong in a harm reduction framework? And do those Americans get to have the choice to choose a less harmful product.

Benjamin Apelberg:
Yeah. Maybe I can just chime in with—I think at FDA, we've been clear that tobacco products do exist on a continuum of risk. I don't think that's a question. And you know, we've obviously authorized tobacco products whether they're e-cigarettes or nicotine pouches, you know. So, you can obviously go and look at those TPL reviews that describe the weighing of evidence that went into those decisions.

But you know, as I mentioned at the introduction, we're really here to talk about evidence related to demonstrating that the particular products that companies want to market do actually benefit adult smokers. Because I think we've talked a little bit about that there is, you know, could be quite a variation in the way that products deliver nicotine, you know, the way that they influence adult smokers. So, it really, you know, really love to hear your all's experience related to these kinds of studies, conducting them, the challenges, you know, like what we can do to sort of provide more information, you know, or guidance to help you along those lines.

Jessica Zdinak:

And if I can chime in here, anybody that knows me in the room knows I could speak on this topic, a very big passion of mine. So, expanding upon that, Ben, obviously under the TCA we know that the specific act states, right, that it requires FDA to deny applications that lack the showing that permitting the product and authorizing it is APPH, right? So, then let's take it a step further. APPH is then further defined as weighing of the risks and the benefits, right, of your product to the population as a whole.

I'm probably going to be the odd one out here because I see both sides of the coin of every single person in this room. So, you know, asking the question earlier about well, isn't it about a relative risk, right, cigarettes to a candidate product? Well, sure. But it's still under the statute says that it's the population as a whole, which is the consideration of users and nonusers. I know that there likely will be a lot of talk about the nonuser aspect, right, because of the risk that was in existence with youth using flavored and other ENDS products. I think really the frustration then became when that starts to pan out and level out and reduce for whatever reason. When can kind of more policy and the regulatory authority adjust their quote threshold of establishing that risk and benefit?

So, if your risk is reducing and you, at one time, should have been—which I agree—conducting the most rigorous study because you have a high risk. But now if your risk is lowered, I think what you guys are suggesting here is that there are other considerations for measuring product use behaviors and switching, right? So, more of the actual use, more descriptive-based studies. But then kind of leading into even again stating that CTP again has the authority and focus on making that APPH determination of the population as a whole, users and non-users, talking about users, with a well-controlled investigational study.

And so, I think where I'm at is—and our team of researchers—is look, in the social and behavioral sciences, there are so many different ways to conduct these studies. I'm an experimental psychologist with a Ph.D. minor in statistics and it's endless. I like to say that it'd be much easier to be a toxicologist honestly, because it's—those hard sciences. So, with the many designs, at what point can we advise folks to say, okay. CTP is likely seeing perhaps the increased risk coming with your product, whether it's a heat-not-burn ENDS product. We're talking about flavored ENDS here. Where does—where do you all stand now, right?

And so, if an applicant comes and says, "We have to demonstrate the benefit to the population." Yes, you do, but there are so many different ways to do that. And you guys spoke to some of those here today. But is the risk still as high as it was a few years ago, which I know when Ryan conducted and just with the randomized control trial, the most reliable study design, Glas, most reliable study design and they have an age-gated device. But how do we, as advisors and scientists, know what you all are thinking in the sense of the risk side to then help us design the benefit side?

Benjamin Apelberg:
Yeah. I mean I will say and then I'll kick it over to you all. I mean this is part of what we're doing in this conversation, right, is to kind of level set to talk about how we've been approaching things. And obviously, the goal of this is to hear from small businesses, to hear about your experiences, to understand them, and to figure out how we can continue to communicate and

articulate further. But I think what you're asking for is what we're—you know, what's happening here is to really have a conversation about this and be able to communicate the—you know, what our experience has been to date.

Jessica Zdinak:
Yeah.

Benjamin Apelberg:
David.

David Portnoy:
Okay. I'll take a stab at this. So, to pull it out a little bigger picture. So, we've heard a lot about how do small businesses know exactly what the standard is? How do we choose our resources? How do we spend our money? And you know, in this area, FDA has been very consistent in what we've talked about in terms of what we see as the factors we're considering, especially for flavored ENDS. That being said, we also try to provide some flexibility. I think another one of the themes has been give us standards, tell us exactly what study to do. And as Lynn pointed out in the last panel, doing so would actually limit your own flexibility because it's not just about any one study. It is really about the multifactorial and multi-disciplinary evaluation. So, in terms of studies of adult benefit, I think the best guidance we're able to give is the stronger your data, even if it overshoots the minimum of what is needed, is going to provide us the best evidence to go on in terms of this really complicated balancing act.

Certainly, we continue to look at the scientific literature over time. And, you know, from my own experience, right, that's something we've sometimes been criticized about. You know, you made this decision in 2021 and now you're making a different one. Well, we have to be able to innovate as well and to update. But we certainly do recognize that that poses a challenge, especially for small businesses. Sarah, do you want to—

Sarah Johnson:
Yeah. I'll just add to that and echoing again what's been mentioned earlier, but pre-submission meetings, especially in this area, can be very effective when you're weighing decisions about what type of study or design, you know, how to design the study. What kind of study arms are you going to have? As you said, you know, with social and behavioral sciences, it's sort of, you know, there's a lot more choices and decisions to make. And so, this has been an area where we have had many meeting requests. And we think it's a really, you know, fruitful decision to take before you make an investment that we understand is, you know, a significant investment.

Bill Wilkstrom:
So, does the FDA have like a 2-week TDY program? Because I would love to invite the FDA down to any of the age-restricted shops where the rubber meets the road. Where you can actually see the adult benefits firsthand and then we can talk to you about how exactly do you want us to extrapolate that data. So you can see with your own eyes and service those customers as to how we can take that data from those customers and then turn around and say, "Okay, FDA, this is what we've got."

Because as he pointed out, these studies are incredibly expensive. So, if you were able to get down and be where the rubber meets the road and get down there and see those customers and see the kind of reaction. Because when you look at—the youth prevention is a very big thing. And I've made it a point since 2016 to work on that stuff. But at the same time I think that's more of a local and state law enforcement issue as far as it comes to. Because there's bad actors who sell to the kids. That doesn't necessarily mean that the appeal is to the youth. The appeal is to convert smokers.

And what we're looking at here—and when you cited the Cochrane study, when you'll see that that's a very high-quality study. And you can see from that study where—that there's high-certainty evidence for nicotine cigarettes increases the quit rates at 6 months or longer. And that's why I'm inviting the FDA. It doesn't have to be my particular shop or shops. It could be anybody here in the entire United States. And you come down there and you actually be inside these shops and see what happens in the interactions with the customers, the actual carding that goes on. Because your own data shows in my state in particular, from 2019 to 2023, the average rate of youth tobacco sales was centered on C stores and gas stations and not age-restricted shops. So, where your real adult benefit comes in is not so much the—I just think that the youth enforcement is really more of a local law thing and trying to adjudicate to see the real studies of the adult benefit is to have people down there where the rubber meets road. So, you can see this and then help us extrapolate what you see and the data that we collect and turn that over to you guys. How can we bridge that gap? Thank you.

Sarah Johnson:
I'll just say that I appreciate you sharing your perspective and that's, I think, the value of us all being here is hearing directly from you about your experiences because you do have a different vantage point. And so, we appreciate hearing about it today.

Eric Heyer:
Can I go next? I've got a lot of questions. [laughs] So, [unintelligible] may imagine but let me kind of run through the laundry list and then you can choose to respond to the ones that you want to or not. First of all, someone just said in running—I call these longitudinal comparative efficacy studies, that's my nomenclature. In running these, someone just referenced the minimum of what is needed. And that's a huge question mark for the industry is, let's say a strawberry flavor in an RCT outperforms a tobacco flavor in terms of reduction in cigarettes per day by an average of one cigarette per day more. Is that enough? Where do we draw the line? Is there some sort of an expectation or some guidance that could be provided around that?

Secondly, the—I'm getting to a second question with this little narrative here in a second. Just to kind of reiterate what Ryan said here. This is all premised on the state of the literature, the state of fact as existed in 2020 and 2021, right? And shortly after the height of sort of the JUUL craze among youth and everything else. And obviously, if we look at the 2024 NYTS, youth usage rates are down 70 percent. Second question is, will FDA go back and reevaluate the assumptions that underlie the longitudinal comparative efficacy requirement based on the significant reductions that we've seen over the last few years in youth usage rates?

Third, I want to highlight that from the perspective of small businesses, FDA has painted with far

too broad of a brush. There is close to zero evidence, pick your brand that open system bottled e-liquids have ever been used by youth in any significant numbers. And we can look at NYTS to demonstrate that. We can look at whatever study you want. Yet they get lumped in with flavor disposables and everything else. And so, is there any comment on that? That's been a major, major gripe of that segment of the industry, which is what a lot of small businesses are.

Fourth, in terms of the study, if it is an RCT, you know, one concern I have about the paradigm that's been set out is this head-to-head for an individual user comparison, I don't think sufficiently, and I'd like to hear a response to this, sufficiently accounts at the population level—and APPH is a population level standard—for the desirability and popularity of flavored products among the population. Per FDA's own statistics, at least 78 percent of adult users use non-tobacco-flavored ENDS products. And let me just give a hypothetical example. If we have an RCT comparing say a banana ice to a tobacco-flavored product, let's say the reduction in average cigarettes per day, a banana ice is six cigarettes per day. Tobacco flavor is eight cigarettes per day over 6 months.

You would throw that application out. You would say it can't be APPH because the tobacco outperforms the banana ice. But then all of the things being equal, if we take 100 cigarette smokers and 30 would use the banana ice, but only 10 would use the tobacco flavor, which is frankly pretty reflective what I think these guys would say you're going to see in the marketplace, right? We add that up. We come to a product at the population level that's a reduction in 180 cigarettes per day for banana ice and 80 cigarettes per day in tobacco flavor. Yet you've already thrown that banana ice application out of the queue.

So, I think that this is an approach that is blinkered and it doesn't appropriately account for the popularity of flavored products at the population level that tobacco-flavored products just don't have. And then I guess the last point I just want to make is I think, the importance of dialogue here is really, really important. Not just pre-submission meetings, but—and it sounds like there's some, you know, going back to the last panel, maybe some good developments in this respect, but if someone goes—a small business goes and conducts one of these studies and wants to have a meeting to talk about the results or talk about, you know, are there changes we should be making or is it worth continuing to pursue this particular flavor versus the other one? A lot of these small businesses will have, have 10 or 15 different flavors. They have to make decisions. Which ones do we call out of our applications? Which ones do we spend several million dollars more pursuing? It would be great to have phone calls and meetings about those decisions because that is—that can make the difference about whether a business is able to be viable or not. So, I think I just wanted to hammer that point. So, anyway, those are my five questions/comments. Thank you.

Mollie Miller:
So, I'll start with the first one. So, the minimum threshold question, I think that was the first one. And we do not have a set minimum threshold of demonstrating adult benefit because a lot of what we talked about today is how the whole APPH decision is multifaceted. You know, there's toxicity that goes into it. Looking at benefit to adults goes into it. I can talk about some of the different characteristics of the data that we look at when making that determination though. And I will use, for example, complete switching as the example here.

And so, when we're looking at data of complete switching, what we're looking at are generally two things to show added benefit. We're first going to look at the overall quality of the study. That goes into how we write the data and our eventual—what we tell the TPL in terms of this was a well-conducted study.

Then we look at the absolute switch rates. So, we're looking at—if you have a tobacco-flavored ENDS and you have your example of a banana-flavored ENDS. How many people switched from the tobacco-flavored group? How many people switched from the banana-flavored group? Absolute switch right there. And then the next thing that we're going to look at is the relative switch rate. So, we're going to compare those two switch rates and look to see does the banana-flavored ENDS increase switch rates compared to the tobacco-flavored ENDS. Those are kind of the three main things that we're looking at. We don't have a threshold, but those are the three kind of main variables that we're looking at when we're looking at the switch data. Do you want to talk about one of the other ones? I can go into the choice.

Sarah Johnson:
Just to address the comments about the youth perspective, which you mentioned that this framework sort of predicated on the height of the vaping issue and use has declined. David mentioned, of course, we're, you know, always following the literature and aware of the most recent data. And you also mentioned specifically differences in youth interest in different types of devices. And appreciate you sharing those perspectives and understand why it would be an area of interest for this group.

Our focus today is on the adult side of it. And so, we're not going to discuss sort of get into detail about the youth side of it but those comments are heard. In terms of adults, so you referenced that the framework posits this emphasis on efficacy rather than what we might call reach, sort of the idea that the population health benefit might be better or more accurately estimated by accounting for the popularity or appeal of the flavors to adults. And so, it is true that the specific studies we've talked about do focus on sort of that question of effectiveness. One reason for that is that what we've communicated is that in this area, we feel like it's important to have the most robust and reliable demonstration of the behavioral benefit. And that is a question we feel like the effectiveness question can be best studied sort of directly in an observable way. That said, this is just one piece of the evaluation. You know, we do have a whole team of scientists, including other parts of the application which social science is looking at, you know, precursors to use that can get at questions of appeal. So, it's not as if it would not be accounted for in sort of the totality of the evidence.

David Portnoy:
And just to add one thing there. So, there was a discussion about, you know, how do you account for sort of this aspect of choice, right? And that really plays into the decision about the study design, right? There are pros and cons of different kinds of study designs, right? And that's something that can be seen potentially more in either actual use study or a cohort study, right, with more naturalistic environment and timeline. But that's going to get at some different kinds of questions and outcomes than a really well-controlled RCT.

And so, that's why whenever you hear us talking about it, we're always talking about an RCT, a cohort study, or other sufficiently reliable and robust evidence. Because we are trying to give the choice of what is best going to serve your goals for your products in order to demonstrate this adult benefit. It's yet another reason why we are very hesitant to set a single kind of study design or threshold. Because again, that is only one piece of the puzzle here.

Jessica Zdinak:
And if I can—real quick, if I can jump in here because I think it's a great segue to something—a point I want to make. So, the PMTA rule and application gets established and there are individuals like Ryan and other small businesses. At ARAC, we work with everybody, small, medium, large size businesses in the industry, I will say, because we're here and you're wanting to hear the small business perspective. I think it's important for y'all to know that there are the small businesses that really just wanted to do what they needed to do to get an authorization. And Ryan, you know, sitting here being one of them, Glas and Kevin and his group and others and, you know, the PMTA and everything that was needed, it's not what they know of. They just wanted to sell a product that then became one that required a very in-depth, you know, process to get authorized. And they came to us and it honestly broke my heart because knowing what we had to tell them that we believe was required is a really, really expensive, time-intensive, resource-intensive, scientific-intensive study. Because—and they're going okay, just whatever we need to do, they want to follow the rules, so to speak. But oh my gosh, what was my point? Gosh, darn it. You were talking about—I'm so sorry. What's your point, David, was about?

David Portnoy:
Choices that—

Jessica Zdinak:
Oh, my gosh. Thank you. Got it. There we go. So, these individuals at that time who were still pending application or scientific review would come to us and have hundreds of SKUs and flavors. The only possible study design, right, because we are now retroactively almost doing a prospective study versus scenarios where a company comes and says, "I have six flavors. Help me in product development to narrow down to three. And then take those three and let's put it into a PMTA." Very different. Certainly we can do those individual randomized arms as you all mentioned, beautiful study.

But when you have 200 SKUs of nicotine strengths and 30 different flavors, the only option is to do kind of a flavor choice. And then potentially not getting the individual SKU data but trying our best, you know, to power it and ensure we have sample. So, what is your perspective and very similar to Eric's question of any consideration of a retroactive review of these applications to say—and I don't mean it quite like that. But, you know, they did the best they could. Some of these having really good study design, but because it's a flavor choice versus an individual SKU randomized, what are your perspectives as far as the validity or the reliability and robustness of those types of designs?

David Portnoy:
I'll start then I'm going to turn it over to Mollie. I mean, one thing I want to make clear is that we very much hear the need and the concern and that these businesses want to comply and are just

saying tell me what I need to do. So, that point, all day, loud and clear. We're not in a position, though, to make business decisions for these companies, right? So, if you're saying, you know, which products should move forward? That's not our decision, right?

And so, if it's about what are the products that show the most benefit, right? Those things are better coming from research development, other partners of these small businesses. Because it's really not our place to say you should develop this kind of product or you shouldn't do another one. In terms of the number of SKUs and the number of products. I mean, this is something we see a lot of. So, as difficult as it is to run a study on 200, 300, 10,000 products, on the other side of it, we have to interpret that same data.

And before I pass it over, one of the things I want to stress is that we do have to make decisions on a product by product basis. And so, what we're really trying to get at is information on that specific product. We cannot issue a marketing granted order for 100 products all at once. And so, from our perspective, what's that balance between the incredibly overly complicated study design and what we actually need for that product-specific evidence?

Bill Wilkstrom:
If I may, since you talked about looking at it that you would be telling us what products to make or not, that's not what we're looking for. What we are looking for is we are looking for standards, clear, concise standards. And I liken that to say, you know, we are making a product just like say a car manufacturer. Just tell us what the standards are for making that particular product. We're going to make that product based off of our own innovation and let the market decide what that does. We are in no way, shape, or form asking you to determine what products to make. We're going to make that ourselves. We just need to know what framework we have to operate in and what the standards are.

David Portnoy:
Understood, and I appreciate that point. I was actually referring to some previous discussions about, you know, if there are five candidate products, could you bring them to us and ask our opinion about which ones would benefit from—okay, it came up in a previous discussion. So, but I hear your point.

Bill Wilkstrom:
Yeah. I would never ask you that because my customers are going to determine what I want to put through the process because those are the ones my customers have determined that they like.

David Portnoy:
Absolutely.

Bill Wilkstrom:
I mean, you guys are just—you're the scientific piece that's looking over saying, "Hey, is this a safe product that we can endorse to be sold on the market?" In no way, shape, or form I'm asking you guys, "Hey, is this, you know, banana ice or this and that?" No, I'm not asking you that at all. My customers have already told me that. I know exactly what they want that—but I just need to know the framework and what those standards are in order to get those products approved and

granted a marketing order.

David Portnoy:
Understood. Let me turn it over to Mollie, who I think was going to talk a little bit more about bridging and other ways to sort of optimize study designs for a lot of products.

Mollie Miller:
Yeah. So, when you're looking at hundreds of products, even in a cohort study, you're going to probably end up with products that aren't chosen or aren't chosen very often. So, you're going to end up with small ENDS even with a cohort study. Again, there's risks and benefits to going that approach. As David mentioned, we look for product-specific information. And at the end of the day, we need to make product-specific determinations. So, while that's one approach that you could take, another approach would be to use bridging. And we know we've talked a lot today about bridging. And something like that would look like if you have a whole host of different flavors, you break those flavors up into flavor categories.

Again, provide justification as to why certain flavors are in a certain category and then you study one of those flavors. And then you provide bridging data to show why all of the other products in that category should be looked at within the same light. So, when we're looking at adult benefit, what you want to show is the other flavors that are within that category behave similar similarly in terms of behavior. So, you may want to look at other use behavior. You may want to look at, if you've done PK studies with these products to look at nicotine exposure is similar among them. Some sort of way to show us that even though we're not doing a longitudinal study with each individual flavor, behavior is going to probably be very similar based on the flavor category.

Bill Wilkstrom:
What I can tell you about that flavor category thing as a shop owner and a manufacturer, you know, we do have sections because it's very easy to divide up your—because taste is very subjective. So, when you look at a customer and somebody—they come in and they want to quit smoking, "Hey, what do I—" My first question would be, "What do you like? Candies, fruits, desserts, what do you dig? You know, berries." And that way I can look at this funnel type system and say, "Well, I like watermelon." Okay. So, now I know you're in fruits. So, that eliminates all of this other stuff and helps streamline the process. And knowing here—listening that you guys are open to helping bridge through flavor category, that's promising.

Mollie Miller:
Yeah. I do want to just note though, that we do need the data to show that the products are bridgeable. But, yeah.

Eric Heyer:
Yeah. Can I go back and rewind the tape a little bit and go back to the, I guess, the response to my comment about will FDA go back and revisit the underlying assumptions that underlie the comparative efficacy requirement? I think I heard you say, well, we're not here to talk about youth. This is about adults. The very reason, if—look at all these TPL reviews, look at the 2021 internal memos done by Dr. Apelberg, right? The very reason for the longitudinal comparative efficacy requirement is the assumption and the data that flavored products are more attractive to

youth than tobacco flavor. So, respectfully, that's a major cop out, I think, to say we're not going to talk about, you know, about youth because that's the whole underlying basis for this requirement. So, again, I sort of want to renew my question. Is FDA willing to go back and reevaluate the necessity of this based on more current data rather than data that's 6 or 7 years old?

David Portnoy:
Yeah. So, I will say we have continued to monitor the literature, update those estimates. So, it's not accurate to say it has not been revisited. Believe me, this is a topic of a lot of discussion. It's not a decision that was made and then put away. And so, we've continued to do that. On the adult benefit side, in addition to the comparative aspect, right, we also want to make sure that these products will be used by adults, right? And so, the benefit of putting them on the market, of making them an option. And so, even if it weren't for the sort of comparative aspect, we would still be interested in seeing the switching, the benefit to adults of these products, right, as yet another line of evidence that goes towards those requirements in the Tobacco Control Act about likelihood of use among different populations that all feeds in with all the other disciplines into that APPH determination.

Eric Heyer:
Yeah. And the reason I raise this is what I think you see a lot with a lot of flavored products in these head-to-head RCT studies without accounting for popularity is both the flavors and the tobacco were both very effective. They lead to dramatic reductions in cigarette consumption and major physiological benefits. But if we're going to have a hard and fast rule that, boy, if they're head-to-head, that's not enough, you're out or if—theoretically, if the banana ice only exceeds by an average of one cigarette per day, you're out. We're not going to look at anything else, which is what we've seen historically, you know.

David Portnoy:
And as Dr. Miller claimed, there are different elements to the evaluation, right? And one is the absolute switch and one is the relative as well. So, so those are being taken in into consideration. Sorry, I interrupted you but I just wanted to get that out before we moved on.

Jessica Zdinak:
Can I jump in, Eric? Yes. So, just using Glas as an example, this has been presented to the public. So, we had 13 to 21 percent cessation rates, age-gated device. So, when we're thinking about the benefit to the population, we're thinking about the smoker. And these rates were above and beyond an already authorized ENDS product and these were flavored. And so, you know, it kind of the best of both worlds where it's actually getting 20 percent cessation from an adult smoker and heavy smokers, by the way, heavy smokers blowing, you know, sometimes 40 and 50 in their ECO. And then we were seeing 50 percent with a significant CPD reduction of 50 percent or more. And so, I guess my question here is that to me demonstrates not only the population health benefit to those that are currently using combustible samples cigarettes. But because it's an age gated, you're also then accounting for the risk side. And I know we don't want to talk about the youth here and look, again, I'm the kind of odd apple out up here, but it's been almost 5 years, right, and they're a product of merit. And so, with a very rigorous study design and so just didn't know your thoughts and I'm sure there are things way above everyone that is

sitting at this table today that can be considered in an authorization. But just kind of wondering when you do have that highest standard to assess the benefit for you all and to make your jobs hopefully easier and still not getting that reinforcement through an authorization is challenging.

Benjamin Apelberg:
Yeah. I'll just say, I mean we obviously appreciate all the comments here. We can't comment on specific applications that are under review. And I think what we've tried to lay out is the articulation of how we've been approaching this population health question. I mean, as you guys know, this is the requirement we have in statute to weigh the risks and the benefits. And a lot of that really relates to sort of understanding the risk to kids, understanding the benefits to adults, and doing our best to make sure we have a proper weighing of that. I think we've, you know, we've clearly heard a lot of perspective on how you all think it should be weighed. And you know, we appreciate that input. That's what we're here for is to, you know, to hear the experience and to hear your feedback. I did just though want to give Dino a chance because, you know, you're on Zoom and I didn't want to forget about you. If there's anything else you wanted to add or comment on.

Dino Baccari:
Are you hearing me okay?

Benjamin Apelberg:
Yes. Yep.

Dino Baccari:
All right. I believe that any meeting that, you know, any important meeting, especially that data, you know, should hold a big part of it leading up to it. And the data is overwhelming, the retention rates, I think that, you know, my friends in the industry, we all share the retention rates are really high. So, as far as a switch rate, I mean it's extraordinary. And Glas, you're going to see more of that. It's just going to keep increasing.

And there's some great companies that were in here, some of which I want to buy from so we can start being prosperous again. But, you know, it's like when I think about like adult, you know, public health and the adult smoker is like, I don't—how did we ever approve a nicotine cigarette? How do we do that? And that's just—when I compare products that have been talked about today from, like, substantial equivalents, I just don't know how they don't get, you know, [unintelligible] be approved and be rushed to market. You know, that's my thoughts and maybe some of my question, too. Thanks.

Eric Heyer:
I just want to go back to the—oh, sorry. I want to go back quickly to the communication point just so my point doesn't get kind of lost. When the longitudinal comparative efficacy requirement came in, if a client comes to me and says, "I've got 25 flavors," I need to figure out what to do the full enchilada on. I don't have enough money to do everything on all of them. Last panel we talked about how expensive and elusive a PK study is, for example.

My advice is go do the longitudinal comparative efficacy study first. Do an RCT and then you

can at least see which have sufficient P values which are going to be defensible. But that—my point is, you know, not to make a business decision about which ones to pursue. But say you do that and there's some question marks around, some maybe marginal results. Okay. Well, you know, there's some that are clearly head and shoulders above tobacco flavor, others are kind of middling, others are clearly below it. You know, having a teleconference or a meeting to talk about the middling ones, and whether, you know, as you're looking at that complete switching data, at the relative switching data, are those worth continuing to pursue or not? That can be a $10 million question for a small business, right? It's not a small thing.

And so, that's what—that is as a, you know, concrete recommendation going forward, that would be extremely valuable to this segment of the industry to be able to have those sorts of meetings and get that feedback, as opposed to just, you know, feel like you're throwing money into a black hole and not knowing—you know. And, you know, there's been some reference to how many products are on the market, you know, that don't have PMTAs or don't have, you know, robust PMTAs. And the reason they're not doing that is because it's so elusive, they don't know what they're aiming at, right? The way to get people into the regulatory funnel is to give them more certainty that if they invest the money, that will take care of the black market issue, I guarantee it. So, anyway.

Ryan Muckenthaler:
To kind of hit on that point as well, you know, I mean, it really was a big risk for us to put forth our longitudinal cohort study. Working with Jessica was wonderful though, and the results were very promising. Our flavored products achieved a 41 percent decline in cigarettes per day from the 600 participants that we followed around for 3 months. So, we were really, really, really excited about that. The study was published in the Tobacco Reporter. And then Jessica, you presented it at Tobacco Science Research Group as well.

So, one of the things though for us is that it does feel like we are throwing money into this black hole. We amended our PMTA application with that study 3 years ago and we have not heard anything since. I know we're not speaking specifically about particular things, but to speak to the struggle of the small business manufacturer here in America is that, you know, any guidance on where our next step is would be incredibly helpful to helping us make those next business steps. In case this is the last time I get to talk, though, I do want to just bring one thing up. Would the FDA ever consider a longitudinal cohort study in a post, I guess, in the post-market rather than the pre-market? And I say that based on, you know, we've talked a lot about standards and if that does become come to fruition, where we can say that we've made our product of this quality. We know that the product is safe. And again, the principle that these products are substantially less harmful. In the consideration of, you know, not delaying harm reduction to adults. And as far as the financial decisions, as well as the accuracy of the data, it seems to a small business manufacturer like me that a post-market surveillance may offer better results for us as well as for the FDA. And that could be something that is, you know, constantly, you know, I guess, regularly looked at as far as, "Hey, it's been 3 months. Let's check your results." Does this product stay on the market type thing? So, would there ever be a consideration for that?

Benjamin Apelberg:
Yeah. I'll just—I'll say that one, I appreciate your comments and the theme that we're hearing

sort of in this panel and all the other panels really around clarity, more certainty to the extent that, you know, predictability, like all those things make total sense. And our goal is to be able to communicate as much as we can as, you know, as we evolve in this process in terms of how we evaluate evidence in order to provide that insight. Ultimately, for a PMTA, we have to be able to make the determination that something is appropriate for the protection of the public health to authorize it. So, that conclusion—that evaluation has to be done before we're authorizing. But I mean, I totally—we definitely hear your guys' feedback and perspective on your challenges.

Bill Wilkstrom:
And here's what I'd like for you to add because you talked about, you know, these are significant investments. And in order for us to innovate, we have to be able to show some kind of ROI, some kind of return on investment. Because if we—who is going to want to invest in you if you have—if you're not even sure what the regulatory process is and what the standards are and what the framework is in order for you to innovate and in order to be competitive in a market-based economy. So, I'm asking you all to consider that these are also significant investments that also may involve investors who are looking for their returns on investment as well. They're not—I don't think that that is something that should—that has not been emphasized enough.

Because in order to innovate and get to these safety standards that you want, you've got to be able to spend the money on the product development. But if we—how can we develop a product if we're not sure what all of those targets are or what those standards are in order for it to attract those investors that we may need. Because who wants to throw $10 million for a study that may get kicked out? So, please keep that in mind. You're talking about significant investments and we only have so much capital to work with. And that's one of the reasons why we have to kind of look towards investors in order to innovate and keep going.

If you look at the amount of flooding that was done over the previous 4 years with all of those foreign disposables, you'll notice they kept continuing to innovate and innovate and innovate while those of us as American manufacturers were stuck in a regulatory nightmare. And it's very tough for us to compete while our markets are being flooded, our businesses being stolen, and wealth being transferred overseas that could have been focused on American jobs and American productivity and innovation that could have benefited our nation instead of our foreign competitors. And I'm asking you all to keep this in mind. We need clear regulatory framework that—so we can actually compete in our own markets. Thank you.

Ryan Muckenthaler:
I just want to say that I appreciate you allowing us to kind of have some comments on this because as you can tell it is a very passionate thing. He's right, though. There—it is very tough to balance the, you know, waiting for the FDA's "soon" in Mr. Todd's words, balancing that with risk of enforcement and continuing operations and continued compliance, it is very difficult. So, I do appreciate the FDA's time and consideration in these matters.

Jessica Zdinak:
Can I say one more thing?

Benjamin Apelberg:

Okay. You get the last word. [laughs]

Jessica Zdinak:
Yeah, really quick. Okay, good. I would also just say very similar to your offer, I guess. But at the bottom, you know, I guess at the base of all of this is the adult smoker. And, you know, being a former—in the federal government formally, and really just having a mission to improve public health, at any point in time, if any of you all want to join, you know, join us. And actually go boots on the ground to see the smoker in their lives and truly how these products—some of these products are impacting them and changing their lives. It really is an incredible story and journey and very emotional. And I think the quantitative data, certainly, we got to have the science to back it up. But the qualitative open ENDS and, you know, hearing the real story is also, you know, attached to some of these small businesses. But thank you all so much for having us.

Benjamin Apelberh:
Yeah. Thank you. I'd just like to wrap up by thanking the panelists, thanking the FDA participants, our participants representing small business. I think we, you know, heard a lot of similar themes that we heard earlier today. But it is really helpful to hear from you guys directly, to hear about your experiences. You know, our goal is to be communicative and transparent and, you know. And so—oh, sorry. Was Dino trying to say something?

Dino Baccari:
Yeah. I'll be quick.

Benjamin Apelberg:
Oh, yeah. Go ahead.

Dino Baccari:
It's just an easy one. Just I think that when people learn of this one is it turns some heads. So—and this is again, third-party verified. Even though we have our own internal lookups. I think the world—and I think maybe some of us here know this, but—you know, from a gender perspective, respectively, from a gender perspective, if we just based it on male, female, the female audiences hovers around—from a large lookup, you know—around 55 percent attempts. And I think a lot—I think it's very shocking number for a lot of people that learn it. And that's totally bona fide.

Benjamin Apelberg:
All right. Thanks for that. Thanks again. And just a reminder that the docket is going to continue to stay open. So, if there are other comments that you didn't get a chance to make today or you know, other data information you want to share with the agency, we'll be reviewing that. I really appreciate everyone's time. And so, now we're going to take a break. Is that right? A 10-minute break and then we'll—

Bill Wilkstrom:
Thank you everybody.

Matthew Farrelly:

Okay, folks. Just want to give you a heads up. We're going to get started. But before we go into toxicological profile, we have a surprise guest who wants to say a few words to just show his support for what we're doing here today and emphasize the importance of this kind of communication, two-way communication between FDA and applicants. So, happy to introduce Dr. Makary, the commissioner of FDA.

Martin Makary:
Thank you, Matthew. It's good to be here. Thanks for letting me pop in for a minute. I just want to say thank you for all the feedback and I know there's been good, healthy feedback. We like that. We like hearing exactly what you think we need to be doing. This is not an agency that belongs to a few of us. This is an agency that belongs to the American people. So, we are here to serve you. And we want to do it in a way that makes sense, that is scientifically sound, and that helps safeguard the public, particularly our youth.

So, keep the good feedback coming. Thank you all of you who have agreed to serve on this panel and come from some far distances. We want to see products on the market that are meeting our standards for safeguarding the public, that are manufactured in a way that we believe is in line with our manufacturing standards for safety, and products that create more competition so that we can see more innovation in this space. So, those are our basic goals. I think we're all aligned. If we turn off the noise of social media and affirming news, we realize we all want the same things. And so, that's the purpose of this and we want to have more of this kind of interface.

So, anything we can do to be available, to give you predictability, markets like predictability, innovators like predictability, manufacturers like predictability, investors like predictability. We owe it to all of those stakeholders to provide predictability. So, thank you for your input and we do take it very seriously and use it to shape our guidance, and also to continue to change the culture in terms of how we view a very dynamic space. Fifty years ago it was just a dichotomous approach to tobacco products. Now it is a very wide spectrum of products out there that we have to think about and think about in terms of how do we reduce the burden of injury from traditional tobacco smoking, and how at the same time, do we safeguard our nation's children? So, with that, I'll say, thank you, Matthew, for your work here today and the team. Thanks for letting me jump in. And I'll be watching the video from my office. We have another meeting now and if I miss any of it, I'll watch all of it on the recording. So, thank you so much.

Todd Cecil:
All right. That is a tough act to follow, so I will do my very best. But I'm thrilled to have had Dr. Makary here and have him do a presentation for you all. That was great. So, hopefully that helps everybody get ready and refreshed for the next—the last but not the least session. So, the ground rules have not changed from our prior sessions. However, what comes next has changed. After this roundtable, I'm not sure if Matthew is going to be able to give us an outline of what we've seen. Things have changed slightly. Our final session pertains to the topic of toxicological profile. Toxicological profile represents one of the sources of risk that we consider in our evaluation of APPH.

The toxicological risk does not in itself determine whether a product is APPH. Just the same as every other group we've talked to, every one of these is taken into account side by side and

evaluated through some rather complex calculus to determine whether or not the product is APPH or not. Instead, this is going to serve as important elements that may increase or reduce the likelihood that a product will be found APPH as these findings will be balanced using that complex calculus.

So, we will begin our discussion with a presentation about what our reviews are looking for with respect to the toxicological profile. We have two presenters for the session. The first is Dr. Hans Rosenfeldt. He's the Director of the Division of Non-Clinical Science and will share the podium with Dr. Mary Irwin, a supervisory toxicologist in the Division of Non-Clinical Science. Both Hans and Mary bring exceptional experience in the field of cancer and non-cancer risk in the tobacco products and have been involved in the evaluation of many ENDS PMTAs over the past 6 years. At this point, let me turn the floor over to Hans.

Hans Rosenfeldt:
Thank you, Todd. So, good afternoon. My name is Hans Rosenfeldt. And today, my colleague Dr. Mary Irwin and I will be presenting regarding the toxicological profile of ENDS devices. Specifically, that toxicological risk is something that ENDS manufacturers can control. The main point of this presentation is that ENDS—let's see am I be able to move the slide. Well, anyway, I'll get there. The main point of this presentation is that ENDS, unlike traditional tobacco products, are wholly formulated consumer devices. Thus, the toxicological risk posed by these products to nicotine users rests solely on the product design of each ENDS product. This fact introduces a lot of product-to-product variability in terms of toxicological risk of ENDS products. But it is also an opportunity for manufacturers to truly make a difference in the harm reduction potential of their products.

So, in terms of the agenda—sorry. I got to take my glasses. Forgive me. We're going to talk about how risk assessment fits into PMTA. We're going to discuss the components of a toxicological profile on cancer and non-cancer. But we're going to focus in this talk more on cancer. We'll be discussing—Dr. Irwin will be discussing some of the new regulatory science policy memos we've worked on in the past couple years. We're going to discuss how product design is key. And we'll give some generic examples of how excess lifetime cancer risk can be calculated and we'll make some final conclusions.

All right. So that—so we're going to talk—before looking directly at toxicological profile, we wanted to address where toxicological risk assessment fits into the overall picture of appropriate for the protection of public health. The PMTA pathway is designed to shape a regulated marketplace by working to move tobacco products towards the lower end of the continuum of risk. CTP assesses an applicant's scientific evidence to determine if the marketing of the new product is APPH, or appropriate for the protection of the public health. To do this, CTP must assess both the risk and benefits to the population as a whole, including both users and nonusers of the tobacco product.

To do this, many different risks have to be taken into account. Risks like abuse liability, initiation, relapse, dual use, and toxicological risk are taken into account along with market conditions and benefits such as cessation or switching to lower risk products to determine if a new product is APPH. Toxicological risk is only a subset of a tobacco product's overall risk and

can be further divided into cancer and non-cancer risk.

Toxicological risk involves a number of different endpoints. These include genetic toxicity and carcinogenicity for cancer risk and health outcome domains described in the PMTA rule and listed on this slide. These outcome domains are respiratory toxicity, developmental and reproductive toxicity, cardiotoxicity, immunotoxicity, acute toxicity, and chronic toxicity. Together, the assessment of these toxicological risks create the toxicological profile of a tobacco product.

The PMTA rule states that a submission must contain the toxicological profile of the new tobacco product under evaluation. This toxicological profile needs to contain information related to the route of administration and to cancer and non-cancer risk as described on the slide, relative to other tobacco products. As mentioned before, these include, but are not limited to genetic toxicity, carcinogenicity, and the health outcomes that are listed here.

As part of PMTA submissions, applicants have included a range of data and justifications for hazard identification, hazard assessment, exposure assessments, and ultimately risk assessments for their new products.

So, what is a hazard that needs to be assessed for an ENDS product? Toxicological hazards may arise from direct addition of ingredients to the product, like flavoring ingredients, or through degradation, combustion, and paralysis of these chemicals. Many harmful and potentially harmful constituents, or HPHCs, are both cancer and non-cancer hazards. During user exposure from an ENDS, all of these toxicological hazards are present in a mixture. Thus, minimizing added ingredients and unintended leachables that are toxicological hazards may lower the overall risks of the products.

Although ENDS in general pose a lower carcinogenic risk than combusted tobacco products such as conventional cigarettes, use of ENDS is not without risk to the user. To give you a picture of what this may look like in an ENDS product, here is a short and non-exhaustive sample of the kinds of toxicants that can be found in ENDS. These are just examples. While some constituents like formaldehyde and acetaldehyde are present in most ENDS, the overall mixture of toxicants that users of ENDS are exposed to varies from product to product. For example, not every ENDS would expose users to high levels of cadmium or pulegone.

Hazard identification is one of the first steps in risk assessment and is critical to the development of tobacco product toxicity profiles because there are so many more toxicants in tobacco products than other consumer products. Toxic constituents present in tobacco products can be very well documented, or they may be less well documented, but nonetheless, have indications of toxicity by varying levels of empirical data. For example, there may be sufficient evidence to list the constituent as an HPHC, but there are constituents that have significant empirical data that have not yet been formalized as HPHCs.

These also have to be accounted for in order to create an accurate toxicity profile for a tobacco product. For example, a carcinogen may have only been recently designated as a carcinogen by IARC. Acrolein is such a constituent. It is on the HPHC list but as a respiratory toxicant.

Recently, IARC has re-evaluated this chemical as a Class 2A, probably carcinogenic to humans, constituent. Another example are constituents that are positive in the Ames assay, which is a highly predictive genotoxic—is highly predictive for genotoxic carcinogenicity. Interestingly, the computational Ames assay model is so good that it has been successfully used in predicting Ames positivity for years in drug regulation, particularly in predicting the genotoxicity of leachables. So, constituents that are positive in the Ames assay, whether the in vitro test or the in silico computational model, need to be included in the hazard identification portion of risk assessments in order to create an accurate toxicology profile of tobacco products.

While it is—it may be tempting to include in a risk assessment only toxicants with the highest level of documentation, such as only HPHCs or only IARC designated carcinogens in a tobacco product risk assessment, such an approach would miss much of the toxicity of a tobacco product. This is because only a very few constituents have this highest level of documentation, such as an epidemiological study or a well-controlled rodent carcinogenicity study. For example, out of 10 positive chemicals, an average of eight or nine constituents are predicted to be actual genotoxic carcinogens that cause tumors in rodents. Therefore, not including Ames positive constituents in a risk assessment would throw out a lot of actual tobacco product risk. And not including Ames positive constituents is not a rigorous approach for defining the overall toxicity of a tobacco product.

To account for these levels of certainty, FDA has used a tiering system in its scientific review of PMTAs to account for levels of uncertainty in hazard identification of cancer hazards, which my colleague Dr. Irwin will describe. While the toxicological profile of a tobacco product entails both cancer and non-cancer hazards, today we're going to—we can provide more detail on managing estimated lifetime cancer risk, or ELCR. We are now going to transition to a short presentation on how cancer hazard tiering can help manufacturers manage the cancer risk posed by their tobacco products. Dr. Mary Irwin will discuss an approach to such tiering, which are described in detail in the FDA Science Policy memos that were recently completed.

Mary Irwin:
Good afternoon. As Dr. Rosenfeldt said, I'm Dr. Mary Irwin. The risk assessment process begins with problem formulation and hazard identification. First, all of the constituents that make up the HPHCs, ingredients, and leachables of an ENDS must be identified, and then we can move forward to hazard identification process. There we will look to determine if any constituents present are associated with adverse health outcomes.

After that, we will look at the specific weight of evidence for each constituent to determine our cancer and non-cancer hazards. From there, we move forward to determine how much of each hazardous constituent a user of the new product may be exposed to, and we determine the cancer and non-cancer risks associated. I forgot to move it. So, there's the risk assessment process.

To identify the constituents that should be moved forward for hazard identification, there are specific types of information that a toxicology reviewer looks for when seeking to determine the risk of the new product. First, we may ask how much of the new product does a user use per day? We are looking for here heavy use assumptions or data provided in the application. In the absence of a 90th percentile of use, toxicology reviewers assume a 40 milligram of nicotine per

day equivalent, and this is based on the heavy use of cigarettes.

Additional information toxicologists would be looking for is information about HPHCs, including the measured levels of HPHCs from a new product and all the available hazard information regarding any HPHCs that are above the limit of quantification or limit of detection. Then we will look for ingredients. How much of ingredients are added to the formulation? Is there any aerosol data regarding those constituents, and all of the available hazard information regarding those constituents.

Lastly, a reviewer will look for leachable studies to determine if there are leachates from the device components or container systems. For example, the coil, wick, or e-liquid cartridge, as well as known hazard information regarding the measurable leachates. To begin our cancer risk example here, toxicology looks at the body of evidence for a given constituent and determines the overall weight of evidence to place a constituent into one of five tiers. Tiers 1 through 3 are defined by EPA and IARC evaluation of known, probable, and possible carcinogens. But as we mentioned previously, if we stop there we would miss a lot of risk.

Therefore, Tier 4 is subdivided based on the strength of available in vivo and in vitro data regarding the genotoxicity and carcinogenicity of the constituent. For example, a positive in vivo assay would be Tier 4A, while positive in vitro assay would be either Tier 4B for Ames positive or Tier 4C for other non-Ames assays. This allows toxicology reviewers to reflect the strength of the data. For example, Tier 4A typically has stronger evidence than Tier 4C and still account for the hazard that's present.

The Tier 5 classification denotes that a constituent is unlikely to contribute to the carcinogenic risk events. Tier 5 constituents are ultimately not added to the cancer risk evaluation. However, there's a minimum threshold for acceptance of a tobacco constituent as a Tier 5 constituent. Namely, if the weight of evidence shows that there's one negative finding for mutagenicity from an in vitro, in vivo, or in silico test and one negative finding for chromosomal damage from an in vitro or in vivo test, and no positive or equivocal predicted outcomes from in silico evaluations, then a constituent could be classified as Tier 5. That doesn't mean that a single negative test in any of these groups can push something to a Tier 5, ignoring positive evidence. This simply is the minimal data that a toxicology reviewer would need to consider a Tier 5 classification. Some examples of flavors we have classified as Tier 5 at this time are on the table here. Note that for D'Limonene, there is a negative Ames, negative chromosomal damage, and negative computational predictions for carcinogenicity. For ethyl vanillin, we similarly have all three elements for Tier 5, but there was also a negative in vivo micronucleus assay that was not used for the weight of evidence because of the lack of target tissue exposure data. For isobutyraldehyde, while there are positive in vitro studies, specifically the MLA and chromosomal aberration studies, there is negative inhalation carcinogenicity study in both rats and mice that are of sufficient quality to push our determination to Tier 5 at this time.

I think it's very important here to note that this is an inhalation carcinogenicity study. Why is that important? Well, as we mentioned earlier, the regulatory provision for toxicological assessments of PMTAs mentions that the toxicological profile of the new tobacco product should be related to the route of administration. One of the largest issues we have seen regarding misconceptions

in the weight of evidence is the use of oral data without proper extrapolation to the inhalation route. As a reminder, ENDS are inhaled products and inhalation bypasses first pass metabolism in the liver prior to systemic circulation. So, evidence based on oral administration may not be directly applicable to the inhalation route. Justification would need to be made to bridge the oral exposure to inhalation exposure, particularly with regards to metabolism in the lung versus the liver, in order to use oral in vivo data to justify a lack of hazard.

So, for in vivo studies specifically for carcinogenicity, it is important to look at—that the studies used have relevant route of exposure specifically in this case inhalation or have solid information for bridging metabolism in the oral study to the inhalation route of exposure. Similarly, for in vivo genotoxicity studies, as I mentioned for ethyl vanillin, the studies per OECD guidance should confirm that the target tissue has been exposed to sufficient levels of the test article. This is because, as I mentioned, first pass metabolism may prevent exposure of the sample tissue to a test article like a flavoring ingredient or leachable.

After the full hazard identification and assessment process is performed, toxicology reviewers move on to the exposure assessment. For exposure assessment, applicant-provided data on heavy use are used when available. But in the absence of such information, 40 milligrams of nicotine daily consumption is the default assumption. After exposure is determined, toxicology reviewers move to the risk assessment and characterization.

A toxicology reviewer will tier the hazards for cancer risk and then move towards calculating the excess lifetime cancer risk, or ELCR, of the new product. It's important to note here that an ELCR is an estimate of cancer risk. But estimating risk is very important when epidemiological data to quantify actual cancer risk is lacking, such as with newer tobacco products. Thus, ELCRs are especially important for ENDS because insufficient time has passed for the conduct of long-term epidemiological studies.

Ultimately, the quality of the ELCR depends on the strength and number of assumptions as well as the overall weight of evidence we discussed earlier. The potential excess lifetime cancer risk can be determined for an individual product. To do this, individual constituent ELCRs are calculated by dividing the daily exposure of a constituent by the potency value. Our memos that are published describe the tobacco-specific mathematical adjustments for inhalation unit risk, or IUR values, when they are available. But in the absence of such values, a threshold of toxicological concern is used. Once the individual ELCR is calculated for constituents, all of the ELCRs for the cancer hazards that are greater than 1 are summed to determine a cumulative ELCR for the part product. This cumulative ELCR can then be compared among tobacco products.

A few notes on calculating ELCR. First, all of the cancer hazards Tier 1 through 4C, including HPHCs, ingredients, and leachables, are included in the cumulative ELCR, unless their ELCR is less than 1. If aerosol amounts of ingredients or leachables are not measured, there is an assumption of 100 percent exposure that is applied to the amount determined in the e-liquid. Also, if there is no adjusted IUR available, the TTC of 1.5 microgram per day is used as the reference value. A cumulative ELCR is a summation of the individual constituent ELCRs and therefore, additivity is assumed. So, synergistic or antagonistic interactions are not captured.

Lastly, the Tier 4D and E constituents are only considered if their ELCR contributions would change the risk management descriptor relative to the marketplace of a 1R6F cigarette. Once the cumulative ELCR is calculated, this value can be compared to the same product category and subcategory. At this time, the ENDS marketplace median of 264 per 100,000. There's also a comparison to other categories as appropriate. And most comparisons recently have been to the reference cigarette as an example of the U.S. cigarette marketplace at 19,954 per 100,000.

For comparisons to cigarettes, toxicology reviewers have used qualitative risk management descriptors to describe the risk to the TPL. As I mentioned, Tier 4D and E constituent contributions to ELCR are only considered if they result in a change of the risk descriptor. So, for example, if you have a product with Tier 1 through 4C of 195, which would make it a lower concern, Tier 4D and E constituents would then change the value to 300 which would be a moderate concern. Then toxicology reviewers would report the range of ELCRs to the TPL for decision-making, noting the uncertainty from the Tier 4D and E constituents.

So, knowing that we can now calculate an ELCR and make the relevant comparisons, what can one do if their ELCR is quite large? One way applicants can control their ELCR is through product design. By using higher quality materials that do not have hazardous leachates and formulating with flavors that are Tier 5 constituents, applicants can reduce their ELCR for their new products. For example, Product A here has an ELCR of 8 from HPHCs and uses BPA-free pharmaceutical-grade plastics for design and therefore has a single leachate that's tier 4C at 0.1 microgram per day. And its flavoring ingredients are all Tier 5. So, the cumulative ELCR of this product is 8 per 100,000.

Compare this to Product B, which has the same ELCR from HPHCs of 8 but uses lower quality plastics. So, leachates like BPA, a Tier 4A constituent, and DEHP, a Tier 3 constituent, are present contributing a total of 900 ELCR. And flavoring ingredients add an additional 200 ELCR, as they are Tier 1 through 4C. The cumulative ELCR of this product is 1,108 per 100,000. While products A and B have the same HPHC profile, the choices made in manufacturing and formulation make Product B present a higher toxicological risk profile compared to Product A. To be clear, both of these products could be APPH, depending on the level of benefit demonstrated by the applicant for these products as ELCR is just one component assessed by the TPL as part of their decision-making. Nevertheless, the lower the ELCR, the greater the chance a TPL can find a product APPH.

So, to provide some conclusions, toxicity of ENDS products does vary from product to product, and the toxicity is largely from manufacturing and formulation design elements that that an applicant can control. Excess lifetime cancer risk calculations can give an estimate of cancer risk and more accurate estimates come with better hazard identification and exposure information. The hazard ID also depends greatly on the route of exposure.

While this presentation focus on ELCRs, the consideration of non-cancer risk is also influential to toxicology conclusions. The way one designs their product ultimately influences the toxicological risks of the product itself. And ways to minimize this risk include using formulation ingredients that do not have cancer or non-cancer toxicities, for example, for cancer

risk, the Tier 5 constituents, and using better quality materials that have innocuous leachates.

Todd Cecil:
All right. Thank you, Hans and Mary. That was great. I really do appreciate it. I think that this is one of those cases where we have done an awful lot to present a standard that folks have talked about. Now I want to be clear that when we talk about a standard, these are standards for our reviewers. All we can do is tell our folks how to evaluate so we're consistent. Because I think there was a question earlier today about getting that one reviewer that is off of—out of normal. This is one of the ways we try to ensure that that does not happen here. Everyone understands what it is, how to do it, and are able to do these sorts of calculations. These have been made available on the website so that you understand what we're doing when we look at your products. We are obviously working on additional ones that we can make available, but they're in process. They're not ready for public consumption yet or not in this case. It needs to get ready for our own internal consumption first and it is not yet ready for internal consumption. But we are working on it, and we really would like to help with more of these sorts of documents as we are able to.

So, with that let me turn to the panel. I think everyone, but one, of us have been on previous panels. But I think it makes sense to go ahead and do brief introductions again. So, let me turn to Steven first.

Steven Haddad:
Steven Haddad, managing member of Breeze Smoke based in Michigan. Twenty years experience in the tobacco vapor convenience distribution space.

Willie McKinney:
Hey, Willie McKinney, CEO of McKinney Regulatory Science Advisors and McKinney Specialty Labs. I'm here representing Custom Technologies. They develop and sell specialized e-vapor products to correctional facilities, jails, prisons, et cetera.

Manoj Misra:
I'm Manoj Misra from Chemular Consulting. I am representing ECS Global, which sells fix ENDS. I've been working in tobacco industry from last about 30 years, big tobacco companies, small companies, and now consulting with Chemular. All different type of products starting from tobacco cigarettes, e-cigarettes, and now pouches.

Char Owen:
Char Owen. I'm the CEO of a small e-liquid manufacturing, Matrix Minds, with an engineering background, and I also consult for PMTA submissions.

Todd Cecil:
Great. Thank you so much. Let me go ahead and open the floor for any questions or comments you'd like to make.

Char Owen:
I have one.

Todd Cecil:
Yeah. Sure. Go ahead.

Char Owen:
Briefly, there was a example list of [unintelligible], right? Does this database exist anywhere where it's available for us? Because I know you don't have—this is a really great thing for manufacturers to have to make those—you know, to do those calculations and say, "All right. We want to leave this chemical alone." So, if you have a way for us to—that would be amazing.

Hans Rosenfeldt:
I think that I will leave that question to Dr. Cecil. Because a lot of this is proprietary information, clearly. And I don't know exactly if there's a mechanism for such information. This—that slide had to be cleared many times in order to be able to put it up here. But I don't know if Todd has any additional information on this.

Todd Cecil:
Yeah. The nice part is that slide—it's in your deck—was IURs which are available on the internet. Those are publicly available sources. The calculation was—all they did is use the calculation that Mary just walked everyone through and just put those up there side by side. So, I think that's just what that slide was. So, there's nothing new or different in it. It's the exact same thing that everybody could do. The question I think that you're asking is, is it possible to make that available? We will look into how that could happen. I think that is something that has potential to be useful. Again, we need to make sure that we are not running afoul of any sort of good guidance practice violations. So, we don't want to put ourselves at risk by looking to the—

Char Owen:
I routinely make those calculations just by what I do. But, you know, if a product—if a manufacturer is designing a product, it would be wonderful if the product never has those types of things. If there's an easy way for the public, for the general small manufacturer to hit that before even gets to the product design phase.

Todd Cecil:
Great. Thank you very much. We will take that with us.

Manoj Misra:
Appreciate that invitation to us. We barely get a chance to talk to face to face. So, apart what I gathered is—this is apart from the education and face-to-face meeting with us—thank you, is also opened a direct dialogue and opportunity what small manufacturer can ask and what FDA can provide as a tool to make our life a little bit easier. So, we're not asking, for example, any different criteria for science for big manufacturers or small. No, science is science for—same for everyone.

So, to Char's point two points for ingredients' tox profiles. So, I'm sure you guys are working for long, long years and day and night to have that and probably available in public databases. But for small manufacturer to create—so 30 SKUs 30 [unintelligible] formulation, 30 to 40 ingredients each, just multiply that number and comes to half a million to $1 million just for the

tox profile. If that can be available to us as a tool for us to assess our ingredient and selection of it and then the level would be great.

Todd Cecil:
Letting someone else answer first.

Mary Irwin:
I would say you saw we did have some of the Tier 5 constituents up there, so clearly we are looking at these things. But as Dr. Cecil mentioned, personally I'd love to shout them from the rooftop. So, I want everybody to use Tier 5 things that are not toxic for non-cancer either. But we'll have to see what we can do through the legal limitations and things like that. But I don't know if—

Todd Cecil:
I was going to add that I think that you know there are—I think thousands might be an understatement of the types and numbers of ingredients that are being added to ENDS products. I've seen individual products that have 15, 20, 30 ingredients. If you multiply that times the 27 million products, obviously there's some overlap. But it's still a lot that we would end up having to take on done that—in creating these. So, I think there might be an opportunity to build a partnership with a standard-setting group to start to do some of these calculations, a CORESTA or an ISO or another group that may crop up to say we'd like to help out, SOT has got all sorts of resources. So, I think you know I'm—I can't suggest who might do this, but I think there is the potential that the industry could come together and work with FDA to identify and help create a resource for the industry. Hans.

Mary Iriwn:
So, the other thing that we should mention for toxicological profiles, data are new every single day and so one of the issues with publishing a toxicological profile is the next day it could change. And I know that's a really unfortunate reality of where we are in the state of the science with toxicology as new things come up. So, in doing that, it would have to be understood that if new data come up, we have to consider that data, especially if it's a big red flag, right? As many of you probably know, things like non-genotoxic carcinogens do exist. Our list is very—looking at a lot of genotoxic carcinogens with Ames assay and micronucleus assay and things like that. But the existence of non-genotoxic carcinogens, I mean we may only find that out after somebody's been exposed and we have to go back and fix after that data become available. So, if we do or are able to do that kind of list, it would have to be a living list and something that would change potentially over time just due to the nature and the evolution of the science.

Manoj Misra:
And we face the same issue every day because the data is coming about every day in new paper. And the second issue we face is we go to conferences and we have a lot of poster presentations and officially presentations there and that is published. What I hear is, of course, it has to have a peer-reviewed publication to be included into our assessment. Lot of cases, those posters, wonderful science, never end up in publication. So, though we have—we are itching for the paper to come out, we know that is true, study was done, we go to conferences, ask questions. But we don't have that in our hand as a publication to cite that and to do our assessment and

that's where we get stuck.

Willie McKinney:
Hey, thank you guys for the presentation. You know, we've heard that it's a totality of evidence that you use to establish APPH. And I think we all understand that. I do think though, I've heard two areas where you can call it standards, you can call it a policy memo, you can call it a reviewer's guide. But where some clarity has been provided and that's the manufacturing with the proposed TPMPs and then here with this ELCR. It might not be perfect, but I can tell you we can do the calculations and look at ingredients and know where we are, right? So, thank you for that.

I think the biggest challenge and the question I have is a list would be extremely nice, a living list. However, there's some applications that have been in the process for a while. Do you apply now this view that you have to those applications? You know, the process just doesn't amend itself to exactly what you were saying. So, how do we deal with that?

Hans Rosenfeldt:
So, just to be clear, is the question do we apply the current approach to applications that were submitted how many years ago?

Willie McKinney:
Well, let me just say that if I recall correctly the memo was made available in June of 2024. Well, there are certainly applications that have been in the system prior that didn't have this knowledge. And those applications may have gone through review and even received deficiency letters and maybe they received a deficiency letter in 2023 before this memo. And they love—they technically can't make changes to the product if according—it would become a new product. So, how do we—how are you applying the memo and how do we address that bigger issue of the small manufacturers want to be compliant. They want to do the right thing. They're constrained.

Hans Rosenfeldt:
So, you're asking a question that has more than one dimension.

Willie McKinney:
Oh, yeah.

Hans Rosenfeldt:
It has dimension number one, being the scientific dimension. But then you have the legal dimension and it's what you people knew at the time. This is difficult for me to answer here in this forum. If Dr. Cecil had any additional ideas on this. But I think that that may be something that we have to take into consideration.

Todd Cecil:
What we want to do is recall that the ELCR memo is a way to try to keep our—be consistent in how we're doing this. This is a system that we have been using. We were using before. We've seen it in applications that have come to us before the memo ever came out. So, this is not a brand new system that we've just created out of whole cloth. This is something we have been

using for an extended period of time.

So, I would suggest that an application that has no not yet begun scientific review will be reviewed relative to the ELCR. Because it is giving us a piece of information that we need to understand to be able to determine whether or not that product is APPH or not. If there is a product that is already halfway through the process and it came out, something happened in 2020 and there was a deficiency letter or what have you, we're going to have to revisit those individually, one by one and figure out where is the appropriate place to apply this and whether or not an initial deficiency letter may be appropriate or not. But I think that is something that we need to address by product rather than as a general application question.

Hans Rosenfeldt:
I would also add that the memos use fairly straightforward risk assessment techniques. So, it's not brand new.

Willie McKinney:
Well, it's not. But it does incorporate the in vitro more so than I've seen before. And so, taking that into consideration, I think. You know, there are some previous assays that have the in vitro data and summarize that and do the risk assessment on the ingredients. But here you've kind of melded the two together.

Steven Haddad:
Thanks. To piggyback on Willie's point, you know, it was refreshing to get that memo because it provided us that clarity and guidance when we were doing our applications. The JUUL TPL referenced an addendum to the memo, but I don't think we've seen it yet. Do you know when we'll be able to get that?

Todd Cecil:
I don't know anything about that.

Mary Irwin:
So, there was an addendum. It was listed in our slides. It was listed and we mentioned it here. This is, I believe, what you're talking about because you said it was in the TPL.

Steven Haddad:
TPL, correct.

Mary Irwin:
And it was an addendum that we did create, and it was signed, I believe it was last July because that's the date that's on the slides. I know we do have a process through which we have to go through with FOIA and then release. And so, I believe right now we're waiting on that process to go out. But I don't know if Dr. Cecil might know more about it than I do.

Todd Cecil:
I do not. I don't know where we are on that. I know that there needs to be requests by a number of people before we can just put it on the website. Again, it has to do with the good guidance

practices and we cannot—if we were to just to come up with a new list and post it up there, there may be a conflict with GGP, which we cannot do. So, we have to be clear about it. If there are multiple requests to FOIA for that information, then we can go ahead and make that available.

Willie McKinney:
We've been made aware that the FOIA office, there are very limited resources within that office because I—probably FOIAed three times myself. So, we understand.

Char Owen:
I have a question. In one of the first panels, there was a gentleman—I believe it was Yang. I'm not sure what his name was. But he had brought up a study where there were—he'd referenced 36 HPHCs, but I believe it's 33. I don't know if it's—what's in that study. And his question, which was misunderstood was much like your tiering system is he wanted to know if there was a standard or a limit for those 33. So, that wasn't the question. So, I just wanted to bring back his question so that it could be answered because I knew it was important to him at the time and it fits within this realm. So.

Mary Irwin:
Thank you so much for that question. I think, as you can see from our ELCR process that we just talked about, we don't really have any limits on anything. We don't set a limit, but we will calculate the risk of that constituent that's present.

Char Owen:
Well, these are like formaldehyde.

Mary Irwin:
Yeah. So, they're considered in the risk assessment. So, I know in your slides, we didn't show it on the screen, but it is in the slides are the adjusted IURs for all of them that are available on the HPHC list. So, that can be helpful. But we do use them in the discussion of risk. So—

Char Owen:
But there's no standard to say if I'm going to pass this point—

Mary Iriwn:
No.

Char Owen:
So, that's a little hard for—like, if I'm—for small business especially, you know. Because we know that those things are bad, but we also know that they're going to come up, right? Because they're in almost every product not in just ENDS. So, is there any possibility of getting any guidelines on that at any point? I mean, because that's a very difficult thing for small business. If they run an HPHC and they come up with, you know, formaldehyde at a certain level, they're never going to hit a cigarette, right? So, you know, because that's—it's going to be astronomical. But we don't really know where that limit is.

Hans Rosenfeldt:

I mean, it does get to the point about risk versus benefit.

Char Owen:
Right.

Hans Rosenfeldt:
And we—you know, there is no set risk. There is a comparison of risk to benefit.

Char Owen:
Okay. So, my benefit is that I'm not quite at the level of the cigarette. Is that where I'm—or is there—

Hans Rosenfeldt:
The benefit would be described by, you know, the—as previously discussed, you know, switching and cessation, those kinds of endpoints.

Char Owen:
Okay. Thank you.

Mary Irwin:
I'll just add for Product A and Product B that I showed you, one was 1,108, right? We did that as it was made up Product A, made up Product B. But you can see, something I very specifically mentioned that both of those could be APPH. It really just depends on all of the other aspects that come together. So, if you have a high level of formaldehyde, for example, using your example, if you calculate the risk and it's 20,000, you might not want to go there. And that's because that's getting pretty too close to a cigarette. So, maybe your risk is very high.

Whereas if you have HPHCs of 8, you know, you might be able to have one or two flavoring chemicals that might have a little risk, but it really depends on your benefit, right? So, the overall picture of APPH requires all of these disciplines that talked to you today. And so, we're just this one little piece, but it's definitely a controllable piece. So, if you, if you see that formaldehyde at 20,000, I would probably feel pretty confident and say you probably should reconsider.

Char Owen:
Change something.
Mary Irwin:
But, but other things, benefits and risks really have to work themselves out.

Char Owen:
Okay. Thank you.

Steven Haddad:
So, in one of your slides, I had thought originally the median for ENDS was 118, and I saw 264 on your slide. Does—two questions on that. Will your descriptors ever change? Like, would you adjust the slide to make the lower concern, you know, less than 300 instead of less than 200 and adjust those numbers or does—is that pretty steady?

Mary Irwin:
So, if you notice on the slide, the risk descriptor numbers did change a little from our published memo and this is because we updated the 1R6F value. So, the risk descriptors are a percentage of the 1R6F. And some of the IURs changed recently. I know some of you may know formaldehyde went up, I think, in 2024, late 2024, so that the actual IUR changed. So, we took account of that and fixed our number for 1R6F. The percentages as it relates to 1R6F, I think I can say, are pretty stable. So, it's as a percent of 1R6F.

In terms of that marketplace number, that's the marketplace as of right now. So, from the original memo, there have been additions to the marketplace. I know you mentioned one, JUUL, and I think a few others have been added since then, since the original memo. So, that's your number as of right now.

Steven Haddad:
Thank you. And then , as part of the overall process, do you guys assign inside—does FDA internally assign weights to particular sections of the application where ELCR would be weighted more heavily than, you know, manufacturing control or vice versa? Do you have anything like that internal internally?

Todd Cecil:
No.

Steven Haddad:
Okay.

Todd Cecil:
No. It really is going to depend. We do give our technical project leads as much information as we can. Our toxicologists will say here's where we are, here's where it is relative to the median value. Here's the risk associated, it's 1 in 500. And our pharmacologists will say there is a low concern relative to the, to the abuse liability. And we're going to go okay, well those two may balance. What is the adult benefit? What is the potential battery explosion? Because if their batteries are exploding or there's no certification of the battery at all, we're going to say, "There's risk here that we need to assess."

So, every application has, its various things we need to consider and so there's no way to apply weighting to it. We have certainly talked about it for years. We picked that one up back in 2016 when we started talking about this. And there is no consistently agreed to way to weight these.

Manoj Misra:
Quick question on risk assessment process. So, I understand the steps. So, it means you—once you identify and characterize the hazard, then it goes to the next phase. You know, multiply by time and exposure and you get the risk and everything's great. And I had a—we had a brief discussion on that before for the in vitro tox [unintelligible], Ames and micronuclei. So, it is nothing but a short-term hazard identification and nothing else. It doesn't tell us anything else except in the whole product, we made the extraction, we expose it for 24 hours or 48 hours and

we got something at the end, is it positive or negative.

But it doesn't go anywhere else. There is no value to it if we don't multiply by the exposure and time to do the risk. So, in risk assessment side, I want to know where the risk this in vitro tox exists. And the reason for that is because about each SKUs—correct me if I'm wrong, Willie, each SKU costs about 35 to 40 grand for in vitro tox and time. It takes about 12 to 15 weeks and about 40 grand for each testing. So, if that component doesn't go to the risk analysis, what it does sitting there as a hazard analysis?

Hans Rosenfeldt:
Yeah. I want to make two points. The first point is yes, Ames and other genotox assays are hazard ID only. That's a very important point. At this time, relative comparisons in these assays are not a thing. However, there is a need. There is a need to assess the overall carcinogenicity of a product. We have assays like the Ames assay that are really very robust. A chemical that is positive in the Ames assay is likely 80 to 90 percent a genotoxic carcinogen. If we were to ignore those chemicals in our risk assessment, we would be throwing out huge amounts of actual risk.

More than that, most carcinogens are not shown to be—or not listed by IARC because IARC and other EPA and other groups can only look at certain number of chemicals at a time. And tobacco products are mixtures of large numbers of chemicals. Therefore, we have to do something. In the memos, we have used the dose response curve based on something like 600 chemicals, carcinogenic chemicals described in Ball et al. And we use that dose response curve as the basis of the dose response curve that you know that we would—of something that is positive in the Ames assay. So, we model that using the database of 600 carcinogens.

So, that's how we handle that. It is an approach. It's not ideal in terms of like—it's not the—you know, the ideal would be to have actual dose response data, you know, empirical dose response data. But, you know, we are moving away from, you know, in vivo approaches. And so, this is another way of addressing that.

Manoj Misra:
Glad to hear that that data is going somewhere. So, I appreciate that. In the tier system, we talked about 1 to 4 and 5 and classification in terms of what if one positive here, one negative there. And this is different combination. So, there are ways—if you do an in vitro study like cell culture study or test tube study as computed, we do animal study for example. So, as a toxicology and chemist there, of course, animal studies carries more weight. It should trump the in vitro. Is that the philosophy you guys have or it's so gung ho on like no, we got one in vitro positive. So, it's just bad.

Mary Irwin:
Of course, we take that into account. So, animal studies have been a gold standard and then human studies, of course, if those exist. Those will provide a higher weight to evidence. So, we're using a weight of evidence approach. Those will carry a heavier weight. As you notice in our certainty tiers, 4A carries a higher degree of certainty than 4B for example, because it is in vivo models. And those might be—you know, in vitro might be a little bit more than in silico depending on the in silico assay.

So, we're not going to say, "Oh, there's one positive. It's good. We're done. We're not going to look at anything else. Not at all." No. We'll look at the total weight of evidence. That said, the in vivo models, a lot of the problem that we have with them is they're oral studies. And oral studies, as I mentioned, the route of administration is inhalation for ENDS. In the oral studies you have first pass metabolism, inhalation you don't.

And so, if there's a good way to bridge from that oral study or if an oral genotoxicity study shows target tissue exposure properly, like the OECD guidance says, and I think ICH S2 (R1) also says that target tissue exposure is key. Because if metabolism happens and you don't have exposure to the target tissue, of course you're going to get a negative because you didn't get there. So, we have to take that into account when we're looking at the oral studies. Is there target tissue exposure, is there sufficient bridging between metabolism potentially, so we don't really have to worry about that? And those are like the two key things with weight of evidence where an oral carcinogenicity study, for example, may not apply to the inhalation route because of those differences in metabolism or an oral transgenic mouse or something may not outweigh an Ames assay because of the metabolism piece.

So, we have to consider all of these things when we're thinking about weight of evidence so that we can feel like—feel good about our decision. We don't want to say everything's bad. You can't put anything in these products. We don't want to say that. We want to be realistic. And I gave you some examples of those Tier 5s where—I can't remember the last one on that list. I think it might have been isobutyraldehyde. Don't quote me. You can look at the slide. Had some positive in vitro studies, but our tiering was Tier 5 because it has a good quality inhalation study. It's actually both in rats and mice. So, the inhalation [unintelligible] is negative. That outweighs all of those in vitro studies because the inhalation [unintelligible] was negative.

But we're not going to ask everybody to do inhalation carcinogenicity studies. That's 50 animals per dose per group. It's huge studies that take 2 years to do. Nobody has time for that right now. So, we'll look at the weight of evidence and we'll try to determine, "Okay. What can we decide based on what's out there and is this going to have potential harm or not?" And if it does, then we need to move it forward and take, you know, appropriate account of that.

Char Owen:
So, you had asked for a small business difficulty, right? And I do have one for you. A lot of times when small business goes, they're using flavor houses or things that, where they can't get—they may get the component levels, but they can't get the amount of those components inside. They may get a range, right? So, less than 1 percent of that and then you can basically do your calculations as to—if it's 1 percent of, 20 percent of, 100 percent of the bottle.

So, that's where for us, things like those standards list or daily exposure rates or something would come in incredibly handy because we don't have access to the master files. You know, we can't get those rates. The flavor houses don't want to give them to us. But we can sometimes get ranges where—so that would be appropriate for us. And I know we've done a lot of research as to how many chemicals are generally used in those flavor houses. And I think we came up with like 630 different unique ones. So, it's not as big of a list as you'd think it was. We have a lot of

access to that data. So, I just wanted to reiterate that sometimes we don't have the data that you need, but we could possibly get ranges that would help us get—make those determinations. So.

Willie McKinney:
Do you guys plan to publish or make public the model, the 600, the dose response?

Hans Rosenfeldt:
It's published.

Willie McKinney:
It's published.

Hans Rosenfeldt:
It's not a model. I should have—it's a publication that establishes the threshold for toxicological dose response curve that was used to identify the amount of micrograms that equivalent to 1 in 100,000 risk.

Willie McKinney:
Okay. So, you were referring to the TTC. Let me ask another question. So, quite a few flavors HPHCs—and this is most important for leachables—do not have an IUI and have very little data. And if I understand the model correctly, it puts those chemicals in the most conservative bracket, right, and although they may represent the smallest amount of the formulation—did I characterize that correctly or did I miss something?

Hans Rosenfeldt:
Well, I'm not sure. What I would suggest is that you know, risk is hazard times exposure or some function of exposure, right. And so, mass matters. And if it's a tiny, tiny, tiny amount, the ELCR component will be less. Unless—does Dr. Irwin have something to add?

Mary Irwin:
A couple of things. So, Ball et al, great paper, I loved reading. It was about 700 chemicals, I think. They took it from the TD50. So, it's not like a BMDL10 and we're not way down at a 10 percent. We're at 50 percent of these 700 chemicals. So, right around the middle in looking at that value based on 700 carcinogenic chemicals. And I will agree with you that if it's a very small component, the ELCR is going to be low. 1.5 microgram is not necessarily making things go crazy unless they're like 27 milligrams, you know, very, very high levels within the mixture.

Now, the only way to really get around that, to be able to actually assess the risk in a quantifiable way would be a 2-year carci study on each chemical and with thousands of chemicals, I don't want to see that done. That's too many animals for me, personally. I would never want to see that done. And I don't think FDA with the reduction of animal use would ever want to see that done. So, really the easiest way to assess the risk is that screening level approach using a TTC as the slope factor. So, it's not that if you have 1.5 microgram, you can't have it in there if it's above 1.5 microgram. If it's 3 micrograms, you're going to have an ELCR of 2 for that chemical, right? Because 3 microgram divided by 1.5 is 2.

So, it's really this the way that we can do a screening level approach to be able to figure out an estimate of cancer risk in the absence of things like these very large carcinogenicity studies or in the absence of epidemiological data.

Willie McKenny:
The challenge is perhaps the number of chemicals that are found. However, if I have tested my aerosol in the Ames, can't I say that this chemical is not contributing to the genotoxicity in this particular formulation?

Hans Rosenfeldt:
I was actually going to point that out as a pitfall—potential pitfall in this area. So, one can take EMS which is usually used as a positive control in the Ames assay and dilute it to the point that it's no longer positive in the Ames assay. Because you've reduced the concentration of the carcinogen or the genotoxicant below the limit of quantitation. That doesn't mean that that EMS solution that is testing negative in the Ames assay is not carcinogenic and is not genotoxic. It means that the concentration is so low that it's not being detected in the assay.

Willie McKinney:
Understood. There's a publication by Hausman that looked at the key drivers of these particular assays. Acrolein is a key driver of the Neutral Red assay. In addition to that, you guys have been clear in terms of how these assays should be conducted, meeting OECD guidelines and hitting the concentrations where you push the assay to see an effect. So, it's a dose response. And so, if the formula was developed so that it is not causing genotoxicity, why can't I leverage it?

Mary Iwin:
Can I ask, do you mean the formulation as a whole?

Willie McKinney:
Yes.

Mary Iwin:
When put into the assay?

Willie McKinney:
Yes. The aerosol.

Mary Iwin:
The aerosol. So, if we look at that, pretty much every ENDS we've seen has formaldehyde or acrolein or acetaldehyde, all genotoxicants. So, if you have any of those in your aerosol, it's a genotoxic aerosol. If you're getting a negative in that aerosol study, I would go back to Dr. Rosenfeldt's point that probably everything's diluted, right? So, you're not taking the most minor constituent that could cause cancer over a lifetime. And then in this assay that's very short term, as you mentioned earlier. Now you have to push the dose to be able to see the genotoxicity in this specific short term, single dose, often, assay.

So, having a negative finding on this whole aerosol in that assay, I'm probably going to say that's

probably diluted because you probably have formaldehyde in there or acrolein. I can look at the HPHCs and see that for many of them and those things should be positive. So, that was one of the things that we discussed in the hazard ID memo as to why we went towards a component-based approach and looking at the individual components and putting things together rather than looking at this whole mixture approach. Because in a whole mixture, you're going to get dilution of things that over a lifetime could cause cancer. And you're not going to be able to see that effect in this short duration assay like an Ames assay or a marker nucleus.

Todd Cecil:
Before we jump in too much further, we are at the end of the session. I would, you know, if you'd like to talk to Mary afterwards, it's great to have her in town. So, take advantage of having her and in your being present and that you can ask more questions. But with that, I would like to say thank you to everyone in the room and like to say thank you to all my colleagues at FDA and the panelists. Once again, I appreciate your time and your input. It was wonderful. And let me turn over the podium to Matthew, who will bring it all to a close for us.

Matthew Farrelly:
Thank you, Todd. Thanks, everyone. I know I'm standing between you, dinner, traffic, airplanes, whatever. So, I will be brief and probably not comprehensive. I was taking notes, I went through my notes. We had a little bit of distraction, a positive distraction with the commissioner showing up. So, that took me away from my assignment of trying to summarize all the main points. But let me hit the highlights at least.

First, let me just express my sincere gratitude to all of you for making the time, making the trips. Also to all of my colleagues in the Office of Science for making this happen. I think it was a successful meeting. It went pretty smoothly. We had some, like I said, some unexpected visitors, which was fun. And it's also been for me, and I'm sure my colleagues, an eye-opening and informative day to hear all your perspectives. You've given us a lot of constructive feedback and a lot of things to consider. While we may not have been able to address all your questions and concerns, trust me, we are taking this all to heart. It's really important for us to hear all this.

I'm coming up on my third anniversary as the Director of the Office of Science here at FDA. And I can assure you that the staff in the Office of Science are dedicated and talented and committed to improving public health. And how we do that is by improving the process. And so, we share the goal with you in that regard. We're dedicated to helping you develop the highest quality applications possible. And today is one of those steps in that direction.

And many of you have highlighted that you got into this business to help smokers move to less harmful products. And I also heard that you want to be compliant to the process to improve public health. You expressed a strong desire to have greater predictability in the process. Concerns not only about the cost of conducting all of these studies, but the fear of missing the mark, such that you'd have to start all over again in a complicated and expensive process. And importantly, a couple of you mentioned that the lack of predictability is a struggle for you to get investors to invest in your businesses, invest in innovation, given the uncertainties.

And then finally, several of you have talked about the challenge of PMTAs for open systems

from both the e-liquid and the device side, from the manufacturing side, because you don't have control over what the other side is doing in that process. So, there's many other things that you all have shared and said about all of the different steps in the process. We will be summarizing this more thoroughly. There's the docket that you can continue to contribute to. We got other comments on that, so we're absorbing all of this.

I know that for you all, you want to see more product standards, more guidance for all of this to make your lives easier, and we hear that loud and clear. And so, we're doing our level best. I know that it's tricky because there's a lot of stuff that's going on every day at FDA that we can't talk about. It's just part of the process. And so, that makes it a bit of a mystery. But I can just say that we are very committed to improving public health. We're committed to this process, and you're all helping us make it better. And just once again, I hear you and I really appreciate you and safe travels back to whence you came.

[end of transcript]