

FDA Approach to Evaluating Nicotine Replacement Therapies 1/26/18

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PUBLIC HEARING

U.S. FOOD AND DRUG ADMINISTRATION

FDA APPROACH TO EVALUATING

NICOTINE REPLACEMENT THERAPIES

Friday, January 26, 2018

9:01 a.m.

Center for Tobacco Products

FDA White Oak Campus

Great Room, Building 31

10903 New Hampshire Avenue

Silver Spring, Maryland

Reported by: Natalia Thomas

A P P E A R A N C E S

Dr. Rachel Sherman, Presiding Officer

Grail Sipes, Panelist

Dr. Celia Winchell, Panelist

Dr. Carolyn Dresler, Panelist

Priscilla Callahan-Lyon, Panelist

Sarah Seager Stewart, Panelist

Speakers

James Boiani, Epstein Becker & Green P.C.

David Graham, NJOY

Dr. Christopher Kocun, GlaxoSmithKline PLC

Dr. Charles Garner, Reynolds American, Inc. (RAI)

Services Company

John McCarty, Intratab Labs, Inc.

Matthew Myers, Campaign for Tobacco Free Kids

David Spangler, Consumer Healthcare Products

Association

Jeff Stier, Consumer Choice Center

Erika Sward, American Lung Association

Dr. Mark Watt, Johnson & Johnson EAME, Ltd.

Dr. Dorothy Hatsukami, University of Minnesota

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Dr. Saul Shiffman, Pinney Associates and University
of Pittsburgh

Ben and Nussy Levilev, Harmless Products Company

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P R O C E E D I N G S

Opening Remarks

DR. SHERMAN: Thank you. My name is Rachel Sherman. I'm a Principal Deputy Commissioner of Food and Drugs, and I'll serve as the Presiding Officer for today's hearing. The purpose of the hearing is to provide an opportunity for broad public input on FDA's approach to evaluating the safety and efficacy of nicotine replacement products.

Before we begin, I'd like to make a few administrative announcements. First, please silence any cellphones or other mobile devices as we on the panel have done, as they may interfere with the audio in the room today. Second, we ask that all attendees sign in at the registration tables outside the meeting room.

Third, the restrooms are located in the lobby past the coffee area to the right and down the hallway, and you will note in the agenda we have two breaks. We have a morning break and then we have a lunch break, and you should have when you registered gotten information about how to order your lunch.

Finally, copies of today's presentations are available on request. The contact information is available at the registration table and will also be for those of -- what is available on the slide. I would now like to ask FDA's panelists to introduce themselves.

MS. SIPES: I'm Grail Sipes. I'm the Director of the Office of Regulatory Policy in CDER.

DR. WINCHELL: I'm Celia Winchell. I'm the Medical Team Leader for Addiction Products in CEDR's Division of Anesthesia, Analgesia and Addiction Products.

DR. DRESLER: Hello. Carolyn Dresler. I'm the Associate Director for Medical and Health Sciences at the Office of Science and Center for Tobacco Products at FDA.

MS. CALLAHAN-LYON: Good morning. I'm Priscilla Callahan. I'm the Deputy Director for the Division of Individual Health Science in the Office of Science and Center for Tobacco.

MS. STEWART: And I'm Sarah Stewart, and I'm a senior counsel in the Office of Chief Counsel of the

Office of the Commissioner.

DR. SHERMAN: Thank you. For media and crews, our press officer is Michael Felderbaum. Michael, can you just -- Michael's standing up and waving. If any members of the media are here today please sign in, and if you have any questions or are interested in speaking with FDA about this public hearing or any other matter, please contact Mr. Felderbaum.

The hearing is intended to give FDA the opportunity to listen to the comments of presenters, so the panelists and other FDA employees will not be available to make statements to the media. Although there are no rules of evidence for this public hearing, there are some general procedural rules.

No participant can interrupt the presentation of any other participant, and only FDA panel members will be allowed to question the presenters. There will be an open public comment period at the end of the day once all presenters are finished. Public hearings under Part 15 are public administrative proceedings and are subject to FDA policy and procedure for electronic media coverage.

Representatives of the electronic media are permitted, subject to certain limitations, to videotape, film or otherwise record today's public proceedings, including the presentations of the speakers.

This hearing will also be transcribed and copies of the transcript can be ordered through the docket or accessed on our website approximately 30 days after the public hearing. And again, we will have that information for you at the registration table and the slides throughout the day.

Today we have 13 speakers registered, and each of them will have 15 minutes to present. After each speaker presents, five minutes are scheduled for the panel members to ask questions. If a speaker finishes early or if the questions from the panel do not take the full allotted time, we intend to move to the next speaker.

That means that speakers may find themselves being called to give their presentations before the time that is listed on the agenda. Although we may be adjusting the speaker schedule as needed, we plan to

keep our scheduled break and lunch time.

For the speakers, this is crucial, we have timer lights to guide you. The light will indicate when to begin speaking and when to stop. The timer will give you a two minute warning before the red light goes on. If you've not concluded your remarks by the end of your allotted time, I apologize in advance, I will interrupt you and I will ask you to do so.

Please remember that this hearing is being transcribed, so be sure to use the microphone when speaking. If you didn't register to make an oral presentation but would like to present your comments at the end of the hearing, you may be able to speak during the open public comment period, which is scheduled to begin at 2:45.

If interested, please sign up at the registration table outside the meeting room by 11:00 a.m. for one of the five minute speaker slots that will be made available.

This is a crucial, again a crucial point for us. We strongly encourage you to submit comments to the docket by February 15th, 2018. Please see the

Federal Register notice for details on how to submit, and the copies, extra copies are available at the registration table.

We take the docket very seriously. We read the comments very carefully. So we do appreciate the time and effort you put into submitting those. The hearing is being webcast live. However, the webcast is not interactive, so webcast viewers cannot comment or ask questions. In closing, I would like to thank everyone including our panelists and speakers for participating today, and I look forward to a very productive public hearing.

In addition, I apologize in advance if I don't pronounce everyone's name correctly. So we will now go to our first speaker, James Boiani, Epstein, Becker and Green. How did I do?

James Boiani

MR. BOIANI: Close enough, that's fine. Hi. I'm James Boiani, and I got the honor of -- I guess I drew the short straw and got the honor of starting first. But I'm a partner at Epstein, Becker and Green. We're a health care law firm that -- and my practice

focuses primarily on FDA regulatory matters and working with various companies on development of new drug products and medical devices. So my statements here are drawn from that experience with regards to working through the regulatory development process.

Now as everyone here can appreciate, you know obviously there's a considerable public health harm that occurs from tobacco products, cigarette smoking, use of other, you know, cigars, etcetera. And so the need to combat this is unquestioned, and I think one of the key points in my presentation is the need for regulatory reform to help speed the development of new products, because ultimately you need a wide selection of nicotine replacement therapies and associated mobile apps and other coaching tools, so people can find the right --

(Off mic comment.)

MR. BOIANI: Okay, okay. So people can find the right, the right solution for them. It's not a one-size-fits-all type of solution. So you need to have that -- have that availability, and to do that, we obviously need to bring more products to market. So my

focus here is on regulatory reform.

The standard for approval is safety and substantial evidence of effectiveness, and you know, anyone who works in the space knows that there's a very wide range of what sort of data can meet that standard. In some cases, it can be, you know, studies and 30 patients. In some cases, it might take thousands. There's really a lot of judgment that goes into how you validate whether a product meets a standard.

So what I'm looking at is some potential alternatives for changing or allowing more flexibility in how those standards are interpreted. And so there are again four general areas I want to focus on. The first is looking beyond the total abstinence end point. Second would be employing study designs which have control arms that are more representative of real world scenarios.

Third is broadening allowable indications to include not just smoking cessation but crave reductions or reductions in relapse, or other benefits aside from just demonstration of smoking abstinence. And then also improving guidance with regards to use of

behavioral coaching technologies. And so I think, you know again, really all of this sort of goes back to looking at real world models and looking for ways to gain some more flexibility.

So from my work with clients, I understand that in the current clinical trial environment FDA is focused on, a total abstinence end point as compared to placebo, which requires complete abandonment of tobacco products for four weeks, a single cigarette during this four week period could lead to patients being excluded from an efficacy analysis.

The approach then leads to a paradigm where for practical purposes people that are likely successful in quitting, that is might have had a slip-up early on in the trial but ultimately will reach a point where you'd expect them to cease smoking, are not included.

What that results in is a powering problem, where instead of maybe a study with 200 patients, you're looking at a study with 600 or 800 or 1,000, to try and get enough evidence in there because you're losing people who have one puff.

So instead of the restrictive total abstinence end point, I think it's important to look at allowing a few of these slip-ups during a trial. Not a lot but, you know, if there's a cigarette smoked in Day 3 or Day 4, maybe a couple, you know, in the first couple of weeks, those patients ultimately if they can complete the trial without smoking more, are demonstrating that I think they really have effectively met an actual abstinence. That's about as good as most people can do.

You know, I think that it's really key to focus on that. I say also too, even though you know any smoking I think we agree is not healthy, there is I think a benefit to reducing to a cigarette or two in a four-week period. If you look at, you know, a standard two-pack a day smoker, they're smoking 1,400 cigarettes in that time frame.

If we're talking about reducing to two, just from an exposure standpoint, assuming that they maintain that one or two cigarettes, you know, every couple of months, that is a clinical benefit, and I think FDA should recognize that as well.

Another issue that's for development, and this ties into total abstinence and total abstinence issue is the use of placebo-controlled studies. This approach has discouraged the use of non-inferiority trials. It discourages the use of non-inferiority trials, integrating comparisons against standard of care, for example NRT patches versus new nicotine replacement therapies, which would be valuable -- which would provide information to users to know which products work better than placebo, basically a cold turkey approach.

I note that many academic and public health studies conducted to assess clinical effectiveness utilize end of treatment point prevalence and evaluate efficacy of treatment using odds ratios. An odds ratio is a measure of association between exposure and outcome.

Utilizing odds ratios to compare outcomes of quitting smoking to active NRTs could be an invaluable tool reflective of how the products will compare in actual use. I think that approach could have considerable value to reducing regulatory burdens in

terms of evidence development.

And finally, I'm relying on the 505(b)(2) pathway. I think greater reliance on the use of comparable bioavailability of products would be helpful. Although the entire product including support, etcetera that come along with that product matter to the overall efficacy, that sort of bioavailability exposure gives you a considerable confidence, I think, in how effective a product would be.

So I think looking to that and relying more on that to help reduce the overall study burns could be quite helpful. I'm sorry. I'm not keeping up with my slides in my rush.

The second, the second issue I'd like to touch on are study design scenarios. Currently, clinical trials include the use of smoking cessation support for both treatment and control arms. For example, in older trials there might be several, 20-25 contact points during a trial, where a patient who's not receiving the nicotine replacement therapies be encouraged to keep not smoking.

Today, similar behavioral tools such as mobile applications, coaching tools for Smartphones, etcetera, might be included in both arms of a clinical trial. But these tools would only be intended for use in the context of using the therapeutic product that's under investigation. Although this approach would control between the arms in a manner to help evaluate that therapeutic effect of the nicotine replacement itself, it also creates a high placebo rate in the control arm, which again brings us to a powering issue.

Powering a study to overcome this placebo effect can be prohibitive in regard to evaluating new technologies. An alternative approach that the FDA should consider would be a trial that provided NRT coupled with any plan support in one arm, versus no prescribed treatment.

Or allowing the use of non-pharmacological routinely accessible tools for use in smoking cessation, essentially allowing for simulation for the real world environment where subjects are picking their control, what they would do in practice.

This would give a realistic picture of the

efficacy of the product in the real world, and given what is known about the benefits of NRT generally it could be provide a reasonable assurance that the products have a benefit that would satisfy both the efficacy and the safety standards for these products.

These are trials that takes a more real world approach in terms of their design has been a recent focus of FDA in several other areas, and this context should be considered as well.

Another approach which may allow for reduced numbers of subjects to demonstrate efficacy would be inclusion of non-inferiority trials with approved therapies. You know, there you would demonstrate non-inferiority to a currently approved product, and look at odds ratios to compare outcomes.

I think ultimately you could see significant data that gives you confidence that the product is effective, or at least as effective as currently available therapies, and again this all goes back to choice.

If two products are equally -- seem comparable in efficacy in a trial, those two products in the real

world some people might gravitate towards one or towards the other based on variety of preferences, and so getting those products to market would ultimately be helpful to the public health.

Another issue that could be new indications for nicotine replacement therapy, abstinence from smoking is clearly the key benefit to nicotine replacement therapy and it's a natural end point. However, other end points can have value as well. For example, as the U.S. battles the opiate crisis FDA has been moving towards a greater flexibility to improve access to safe and effective therapies.

I think as Commissioner Gottlieb recently stated with regard to opioids and other substances abuse, FDA is planning to issue guidance for product developers as a way to promote development of addiction treatments. As part of this guidance, FDA will clearly lay out our interest in development and use of novel, non-abstinence based end points as part of product development.

It will also aim to make it easier to develop new product that address the fuller range of symptoms

of addiction such as craving. I think that thinking in that model would also be -- serve nicotine replacement therapy development well. Again, this is consistent with recent FDA approvals. For example, FDA recently approved a de novo application for a medical device called the NSS-2 bridge as a aid in reducing the symptoms of opioid withdrawal.

Reducing withdrawal symptoms was understood to provide some inherent benefit and clinical value, and served as an end point in the study that was the basis for that approval. I think this reflects an understanding that with the reduced effect of withdrawal symptoms or craving or however you'd like to characterize it will ultimately help translate the clinical benefits.

One potentially valuable indication in the NRT specifically as were alluded to is craving reductions. Similar to reduced withdrawal symptoms, it would be helpful to allow a reduction in patient's cravings, particularly during the first two weeks of an attempt to quit when the cravings are greatest, and someone's really getting into the mind set of quitting.

Smoking status during the first two weeks in NRT therapy is highly correlated with the successful treatment of smoking addiction. Any help during that time is likely to translate to better outcomes for patients.

Another potentially valuable indication for products would be to help recover from relapses. Many people have slip-ups as I noted during attempts to quit, but ultimately are successful in quitting. However, there might be multiple points where there's, you know, there's some smoking and how do we get people back on track.

Having a product design to address those relapses and getting in indications specifically for that use could also be a very useful tool, both in getting products to market and helping patients by filling a need.

Fourth, I wanted to touch on behavioral coaching tools. There's been a proliferation tools due to the hands-off approach of the Center for Devices in regulating these sorts of products, with the release of the mobile medical apps guidance in 2015. These tools

can provide more convenient, tailored approaches to receiving support while using NRT, while replacing the traditional phone bank support model.

However, there's been confusion within the industry with regards to how CDER views these products in practice, and whether they might be viewed as conditions of use that integrate them into the whole NDA approval, subjecting each software update potentially to an NDA supplement.

I think what we need to do is avoid that and have a similar approach allowing flexibility both in trials and ultimately in approvals, that allows for the same sort of flexibility and design rollout of new mobile app coaching therapies that CEDRH has adopted.

And then I think in all, I would say with all of this, it's going to be very helpful, particularly on this last point, to provide new guidance, and the guidance should I think be reflective of the need for flexibility, should help try and address some of these concerns, for example with regards to mobile app development in the drug approval context, and ultimately help try and facilitate bringing more drugs

to market through flexibility, end points and indication, etcetera.

And again, this is a quote that my original boss told me and I steal from her continually, because she stole it from Voltaire. The perfect is the enemy of the good. We need a flexible system that allows vendors to innovate, and that's my presentation.

DR. SHERMAN: Thank you for your thoughtful remarks and concluding on time. Are there any questions from the panel?

DR. DRESLER: Can you clarify something that you had said at the start, and you can tell me -- since you're an attorney background, maybe it's not a fair question for you. But I thought did you say that if you were smoking two packs of cigarettes a day and going down to one to two is good enough?

MR. BOIANI: I didn't -- well, I wasn't saying it was necessarily, but I was -- there were two points I was making. One is the occurrence of a cigarette or two cigarettes in a trial is not unexpected, particularly at the early stage while you're rolling in. So counting that against an assessment of

effectiveness is probably not okay.

And then with regards to the second point, again I think if you had a reduction, again this comes more from my environmental or my lawyer background. But if you had a reduction from 1,400 cigarettes a month to one continuously and that was maintainable, would that be a clinical benefit?

I think some would say yes. That's more my personal opinion, but again just from working on issues in the environmental space with regards to exposure, that sort of dramatic reduction might have a benefit itself.

DR. DRESLER: Thank you.

DR. SHERMAN: Other panelists?

DR. WINCHELL: Sure. I wanted to ask just a little more about the -- you were concerned that patients with slips in the first couple of weeks of treatment would be adjudicated as non-successful in the analysis.

Currently, all clinical trials employ grace periods of as little as two up to as much as say nine to twelve weeks before the adjudication period. So

were you concerned that's not long enough?

MR. BOIANI: Not necessarily. I mean I think maybe in some cases sponsors have had a different impression with regards to the standards, and again this is in part informed by my conversations with clients. So I think this ties back to the need to have clearer guidance from FDA, so maybe that is a misimpression in some regards. Or -- and maybe in some cases it could be justified to allow a greater slip-up period, you know, if the science supports it.

But I think in talking with folks, there was that impression that slip-up in the first two weeks might actually lead to exclusion, and I think that's -- that would be a great thing to clarify.

DR. SHERMAN: Other questions from the panel?

DR. DRESLER: I have one follow-up. So you mentioned the 1,400 down to one or two, and then and you talked a little bit about sustained substantial reduction should be in itself be considered a clinical benefit.

Would you be able to submit to the docket the data on which you base these conclusions? And also,

any data you have on, if you will, the grading 1,400 to 2, 1,400 to 20, that sort of information. Any quantitative data that you have would be very helpful to us.

MR. BOIANI: Sure, absolutely. And again, I don't want to focus on that point in particular. I think ultimately the goal is to cease smoking and I think addressing the issue with regards to the slip-ups and how those are treated is obviously the best way to go. Just the point I was trying to make, and I will submit additional data with regard to this point, is that from an exposure standpoint, assuming that can be sustained.

I think there's some evidence out there that might suggest that is actually in itself a clinical benefit. But I will be happy to submit that.

DR. DRESLER: Great. Thank you very much.

MR. BOIANI: Sure.

DR. SHERMAN: Thank you for your remarks. Our next speaker is David Graham from NJOY.

David Graham

MR. GRAHAM: Thank you Dr. Sherman, panel. My

name is David Graham. I started working with nicotine replacement therapies some 25 years ago with Pachkum (ph) and Hailer (ph) and others. I brought up some four years ago began working with electronic nicotine delivery systems, especially with NJOY and then as a consultant to various companies, and now with NJOY's chief impact officer.

I'm also a principal investigator on NJOY's contract with National Institute of Drug Abuse for the development of a research ENDS device that largely is a focus of this presentation. I'd like to begin really with an outline of my presentation covering three areas.

First of all, I'll make reference to what I suggest is a helpful framework that takes into account important context for today's discussion and for the panel's deliberations. Secondly, I'll present some new data focusing on PKN satisfaction (ph) for an electronic nicotine delivery system, and by necessity this will be limited in scope due to time constraints.

But more complete data will be immediately available to FDA, and soon to be filed updates of our

existing tobacco product master file and drug master file for this product, followed by an update to that drug master file.

Thirdly, I'll offer some additional remarks concerning opportunities concerning the evaluation of efficacy and safety of therapeutic nicotine replacement products, and how we may -- and how FDA may foster innovation in this area, leading to increased public health impact.

So Abrams et al. have recently proposed and published a framework for nicotine-containing products within three dimensional conceptual space, with harmfulness on the X axis, appeal or popularity on the Z axis and satisfaction, which includes degree of dependence, on the Y axis.

They note that appeal is related to satisfaction, including factors such as nicotine levels, taste, flavor, sensory characteristics and dependence liability. This vigor provides a road map with which to envisage where a specific class of products may be placed.

The top front right corner depicts the most

appealing, highly satisfying and most toxic space, where combustion products are located, and the authors note the bottom front left space depicts the low toxicity, low appeal and low satisfaction, where they locate NRT. They suggest that for products to successfully compete with smoking, the sweet spot is depicted by high appeal and satisfaction, but relatively low toxicity. This is where they place e-cigarettes.

This begs the question can end products better deliver nicotine closer to smoking, and provide greater satisfaction than currently approved therapeutic NRT? To address this, I'd like to present some results from a recent study.

This study set out to evaluate the comparative pharmacokinetics of nicotine of NJOY's ENDS product, which was developed as part of a contract with NIDA for research. The study, funded in part by NIDA, was conducted in the U.S. and involved administration to smokers of the research ENDS, smokers on brand combustion cigarette and an NRT nicotine inhalator from the UK, which is comparable to the FDA Nicotrol

inhaler, as well as administration of research ENDS and subject's own brand ENDS to experienced e-cig users.

The study included a ten inhalation fixed dose and a six hour ad lib session, and included evaluation of safety and tolerability, effects on craving and user satisfaction, evaluation of various biomarkers and was conducted to GCP. During a limited time period today, I will focus on some of the PKN user satisfaction data.

Here's a logarithmic plot of the plasma nicotine concentration from the initial fixed dose session in the smoker group, illustrating that the ENDS device delivered significantly more nicotine than the inhalator and less than smoking.

Note the research ENDS resulted in a Tmax, which is qualitatively similar to the plasma nicotine profile seen after cigarette use, suggesting long delivery of nicotine, while the Tmax for the inhalator was much later, probably due to its buckle and operator way delivery.

Of note, all subjects were current smokers but not experienced end users, and it's been noted elsewhere that experienced end users become better able

to gain increased levels of nicotine from ENDS devices. This was also seen in this study as follows. Here is the data concerning nicotine concentration in experience vapers for the research ENDS, and also compared to subject's own usual commercial ENDS device.

You see increased levels of nicotine much closer to that from smoking. The study confirmed that the research ENDS made a goal established by NIDA for this ENDS product to achieve a plasma nicotine concentration of at least 15 nanograms per mil within 30 minutes of use.

A brief look at the ad lib session in the smoker groups shows the ENDS device delivering nicotine significantly higher than from the inhalator and below that from smoking. For the experienced ad lib session, nicotine levels achieved by the ENDS device were higher than those seen here, and at levels comparable to smoking.

I'm not showing that slide here for brevity, but ask the question if ENDS can be shown biochemically to improve on nicotine delivery versus NRT, what's the subjective assessment for smokers concerning nicotine

and other elements of satisfaction in relation to these products or this product?

This slide shows the response by the smoker group to a five point rating scale concerning delivers right level of nicotine. The bottom two ratings and top two ratings have in each case been combined, and in this case, I want much less and I want somewhat less on the bottom, and I want somewhat more and much more on the top.

As you can see, the sweet spot has twice as many smokers rating the ENDS device about right versus the NRT inhaler, with most smokers satisfied with the ENDS device but not from the inhaler.

Not surprisingly, these figures or findings are consistent with the effect of each product on smoking arches (ph), where here you see the largest reduction in smoking arches achieved by the combustion cigarette, top line in black, the ENDS device closely behind, in green, and the inhalator in red having the least effect.

This finding is consistent with subjective ratings of reduces craving, where most smokers were

dissatisfied with the effect of the inhaler, while more than 70 percent of smokers were collectively satisfied or very satisfied with the ENDS device. Here you see satisfaction with taste and flavor, and again the ENDS hit the sweet spot, with more than 80 percent of smokers not being satisfied with the inhaler.

And finally, on this section here you see overall satisfaction compared to a regular cigarette, the ENDS device again mostly in the sweet spot, while most smokers were dissatisfied with the inhaler. Now while this is only an abbreviated snapshot of the data, I hope we can all agree that in any consideration of the potential for improved therapeutic NRT products for smoking cessation, they should include serious consideration of ENDS products such as this.

Whether or not that potential can be realized is precisely why we're all here today. FDA's commitment to consider how it might evolve its regulatory policies to enable such opportunities is really to be applauded, and I'd like to move now to some specific suggestions to the Committee in its work.

In consideration of efficacy, this is directly

dependent on hitting the sweet spot of nicotine delivery, no less than currently approved NRT, and as much as smokers are used to from smoking. This concept of pharmaceutical, a pharmacokinetic bracketing is already well established in the UK as a result of a policy shift by the MHRA many years ago, and removes the obligation for multiple time-consuming and expensive cessation studies for products that demonstrate delivery within this therapeutic window between the approved nicotine replacement therapy, delivery and the nicotine expected from cigarette.

FDA has an opportunity here to take a similar approach. If PK is not enough, it can easily supplement, be supplemented by evaluation of craving reduction as a surrogate. Turning to safety, the question for a cessation treatment should not be limited to what is the effect of use in comparison to no use at all, but rather how does the product safety compare to smoking and its consequences?

According to the National Academy's report on e-cigarettes released this week, there's conclusive evidence, and I quote, "that completely substituting e-

cigarettes for combustible tobacco cigarettes reduces user's exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes.

Surely FDA can agree that at least in a limited duration of use for treatment, there can be no other conclusion. FDA CDER has shown reluctance in the past to take into account the consequences of continued smoking as a comparator to the risks associated with nicotine replacement therapies in setting expectations for safety.

I respectfully suggest that FDA consider amending this position in light of the conclusions of National Academy's report, the many like-minded representations it had during its last workshop on this topic on NRT around 2012, which are a matter for record, and the additional representations that I expect you will likely hear today.

Finally, I call on the Committee to seek a balance of sufficient safety that takes into account the importance of satisfaction. To be clear, a benign product that's unappealing such that smokers won't try it or unsatisfying such that it's quickly rejected is

not going to change the world. A singular focus on nicotine delivery is inadequate.

ENDS products that offer demonstrably greater satisfaction than NRT are already more widely used for smoking cessation than currently approved NRT in many areas. Appeal and satisfaction matters, and by expanding reach, which is a necessary factor in ultimately achieving public health impact. I thank you for the opportunity to present to you today, and wish the Committee every success in its deliberations.

DR. SHERMAN: Thank you for your remarks.

Questions from the panel?

DR. DRESLER: I do and I'm trying to think how to phrase it concisely for you. But one of the things you alluded to at the end is that the cessation product should provide satisfaction.

DR. GRAHAM: Yes.

DR. DRESLER: And so usually that means addiction, persistent addiction. So not only is it satisfying because it reduces craving, but the other thing is that it tends to have longer-term use, right. So satisfaction, persistent addiction. So one of the

things that I wonder about, are you -- because let me go back then after saying that.

When you designed this trial, so you know with the what's called the inhaler, only like nine percent of it goes into the lungs, right? So instead of using the nasal spray, which has a much faster and more rapid higher nicotine delivery. So I was kind of puzzled why you picked the inhaler for that study versus a cessation product that's on the market, but it's prescription, as is the inhaler in the U.S., right?

But so then I wonder, are you asking the FDA then, and I'm going to put the CDER since I'm a CTP right? So are you asking the FDA to approve a product that delivers nicotine as well as a cigarette does, that potentially has lower harm, that's going to be persistent long-term use, addictive, and are you asking for that to be prescription or OTC?

DR. GRAHAM: Firstly to your point on comparison to other products, the decision was made to use the reference product as a product that also delivers nicotine closer to -- as close as it exists today to inhalation, which is standard in the guidance

from the MHRA.

I should note that NJOY has actually a file under review that has been validated as a marketing authorization submission to MHRA for this product as a smoking cessation product, and that was one of the reasons that we chose this particular product as a reference.

I think the question you raise as to how high to go in nicotine is always a challenge, and I think it's presumptive to believe that that necessarily leads to long-term addiction. In a world where the product is guided in its limitation of duration of use, which is where most NRT started, I think there is an opportunity for FDA to consider a framework which takes into account the potential for these products to help people stop smoking within a defined treatment period that may be as limited as 12 weeks, where FDA initially is at, and then encourage cessation of that product at that time.

DR. DRESLER: If I can follow-up, but most studies show people do continue to use, both the oral products and for example nasal spray. I mean that's a

significant problem with the nasal sprays, that it does have some longer-term use after the six months. So and then maybe that's not proper public health, because you recommended comparing that to persistent cigarette smoking, which kills over half the people who use it, right?

So maybe that's why I'm trying to understand, is it a -- are you asking the FDA to say that, for example, ENDS or NJOY could be used long term and that's -- even if they use it long term, and let's say I don't know, two years, I'll make that up, that that still is better than cigarette smoking? Is that what you're asking?

DR. GRAHAM: I would disagree with your suggestion that most people continue use of nicotine replacement products long term. The challenge is that most people don't use them very long at all, and part of the reason for that is the lack of satisfaction that they provide. I think the Agency has the opportunity to consider fundamental policy changes that would allow it to consider opportunities such has been proposed in this area.

But in its current framework, we have heard many times from FDA over many years that what I'm proposing today is not yet viable, even though it is considered to be so by other agencies such as the MHRA, and therein lies the opportunity.

DR. SHERMAN: Other questions? Ms. Sipes.

MS. SIPES: Yeah, I just wanted to clarify one thing that you said. I understand your point about NRT use. Were you saying that nicotine, there's a question about how addictive or satisfying nicotine product would be long term, or what is your position on that?

DR. GRAHAM: Could you frame the question again?

MS. SIPES: Hypothetically, if you think of a nicotine product that is satisfying in terms of its delivery, do you have any question about the addictiveness of that product?

DR. GRAHAM: I'm not going to deny that nicotine is addictive and that the level of addiction is in many ways dependent on the route and speed and amount of nicotine that is delivered. The opportunity here is to explore nicotine delivery at lower levels or

up to the level of a current product that would be alternative tobacco product or cigarette that we're trying to replace. I wouldn't suggest that we look beyond that.

DR. SHERMAN: Other questions? I have a couple of follow-ups to Ms. Dresler and Ms. Sipes. First in terms of the level of nicotine that is ideal and the sweet spot, how were those data developed? PROs? How did you choose the ideal spot, the level?

DR. GRAHAM: Well in this particular study, the evaluation really was to identify what nicotine was delivered. The ideal set by NIDA, 15 nanograms per mil within 30 minutes, was relatively high, really corresponding with levels seen in cigarette smoking. Thirty minutes was a fairly long duration to achieve that peak. It is more commonly seen in five to six minutes in cigarettes, which is in fact what one saw in this study.

DR. SHERMAN: And do you have any data, would you be able to submit to us anything about duration? In other words, should that, if you will, ideal level be sustained, tapered? Do you have anything like that?

DR. GRAHAM: I think therein lies an additional opportunity for FDA to consider how it may facilitate access to products such as this for longer term studies by independent investigators. As I'm sure the Agency well knows, they have been reluctant to allow independent investigators to conduct longer term smoking cessation studies.

Part of the challenge lies in the IND. NJOY is working with NIDA to help provide the necessary support for an IND. But as long as the Agency continues to take a position in looking at safety requirements even for a smoking cessation study that requires animal toxicity in two species, it's very unlikely that anyone is going to see INDs granted for such products in the near term.

So I agree with you. We need more long-term data, and I'd encourage the Agency to be more pragmatic in its expectations for what would allow these to proceed.

DR. SHERMAN: So one related question then. In your opinion, what would be the appropriate safety comparator? Is it someone who smokes combustible

cigarettes? Is it something else? What is -- how would you see the -- on what basis would you see the Agency considering the safety and making a risk benefit decision?

DR. GRAHAM: I would say that a fundamental shift in policy that the Agency has an opportunity to make, is to recognize that the alternative to someone using these products is in most cases to go back to smoking and the continued effect of smoking, and that harm should be taken into account in comparison to someone being able to use either a new product for smoking cessation or considering the expanded indications of even existing products.

DR. SHERMAN: Thank you. Any question? Thank you for your remarks.

DR. GRAHAM: Okay.

DR. SHERMAN: Our next speaker is Dr. Christopher Kocun, Kocun.

Dr. Christopher Kocun

DR. KOCUN: Thank you and good morning everyone. Thank you, Dr. Sherman and the panel, and the FDA for the privilege to present this morning. My

name is Dr. Christopher Kocun, close enough, and I'm the chief medical officer for GlaxoSmithKline Healthcare. It's been over 20 years now since GlaxoSmithKline Consumer Health had obtained OTC approval for our nicotine replacement therapies, both Nicorette gum and the NicoDerm transdermal patch.

These products have helped a great number of smokers with their goal of smoking cessation, as you've already heard earlier this morning by other speakers. However, we're here today and we thank the Agency for recognizing this, is there's still a long way to go to reduce the negative public health consequences of tobacco use.

The current trends in smoking are still estimated by most published authors to lead to approximately 10 million deaths in the next 25 years in the United States. This morning I'd like to take the opportunity to provide GSK's perspective of how we might further advance the utility of current medicinal nicotine replacement therapy in helping the millions of Americans who want to quit smoking.

It's especially important for those suffering

today from a smoking-related disease who are quite desperate to quit and need assistance. There are key principles that must be remembered as we consider our options going forward, and they are the public health goal is in cessation of tobacco use and ultimately abstinence from nicotine itself, and the scientific standards that must be maintained to achieve that.

We at GSK believe that there are opportunities for the use of NRT for smoking cessation to evolve, and hopefully keep pace with the changes that are occurring on the tobacco side. These opportunities include, but are certainly not limited to the following: Expanded label indications for current NRT products; the potential for using a combination of NRT products to improve efficacy and even the development of a more flexible, faster-acting forms of nicotine replacement therapy.

We also believe that these changes can be accomplished much more efficiently by building on the knowledge and experience gained from the 20 plus years of availability of the OTC nicotine replacement products today, both here in the United States as well

as abroad.

The public health consequences of tobacco use are very well known, and as a physician the reality of the impact is frightening to me and others. As the slide states in bullet one, a recent Health and Human Resource report states that approximately half a million U.S. citizens are denying each year from a preventable death and disease due to smoking.

While great progress has been made in reducing smoking cessation rates and accelerating the successful attempts to quit smoking, I think we can all agree the challenge still remains. Cigarettes, combustible, are an extremely efficient device designed to rapidly deliver nicotine and their effectiveness in delivery both creates and maintains addiction to nicotine.

The reality of continued tobacco dependence makes the need for additional effective smoking cessation a goal for FDA, public health advocates, the health care industry and most importantly of all smokers today who suffer the consequences of tobacco dependence.

There have been enhancements in flavor and

forms of NRT, for example the addition of lozenges and mint flavored gums, as most of you are probably familiar with. These modifications have helped to improve both product appeal and foster improved dosing compliance. However, the basic elements of monotherapy and duration of use for NRT in the U.S. remains unchanged.

The appeal of a single change such as reduce to quit or using a combination of NRT forms still requires today the completion of one or more randomized placebo controlled trial with the 28 day continuous abstinence as one of the primary end points. Markets outside the U.S., as you've heard from both of our first two speakers, and you'll hear now from myself, have already expanded NRT use to include such things as reduce to quit, temporary abstinence and combination therapy.

Some markets also include specific instructions to use NRT for periods up to 12 months to maintain abstinence. Citing published literature and following the recommendations of expert panels, many markets have fully accepted the basic premise that

there are no circumstances in which it is safer to smoke than to use NRT.

Expanding the role of nicotine replacement therapy must continue to require though scientific rigor. But we should also recognize that no two smokers are alike, and flexibility is an essential element in creating nicotine replacement therapy improvements and expanding indications. It may be misleading for NRT to be considered strictly just the replacement of a form of nicotine.

As I stated briefly before, cigarettes are an extremely efficient delivery device for nicotine. Current NRT forms cannot match the nicotine delivery characteristics of cigarettes, and inability to mimic the nicotine delivery effects of smoking cause many smokers to abandon their attempts at complete cessation.

True to their designation as NRT or nicotine replacement therapy, the ability of these products to address the speed and frequency of craving relief is critical to their utility as smoking cessation aids. Studies have shown as-needed basis of use of product,

for example, is more closely aligned with how individuals smoke today, and therefore may have the potential for a more successful outcome of achieving sensation.

That is why a focus on potentially faster craving relief and dosing flexibility may prove extremely beneficial. Offering smokers more sensation options is also important. A new indication, for example using reduce to quit instructions where smokers gradually reduce the number of cigarettes per day, and then quit may appeal to a significant number of potential quitters, who may be less motivated to quit at the onset of treatment.

As we all know, it is a journey to quit. Trial results show that a less motivated population can result in a lower number of absolute quits or sensation. However, the placebo versus active results were some of the highest observed in follow-ups with study participants showed an increased interest in actually attempting to quit again.

It is also very important to note that an individual's dependence on nicotine may require

nicotine replacement therapy for an extended period of time. Many markets outside of the United States allow or encourage use for periods of six to 12 months of nicotine replacement therapy.

The clinical practice guidelines on smoking cessation drafted under the auspices of the HHS agency for health care policy and research, also endorsed the potential benefits of longer term use and noted the safety profile and relative abstinence of dependence on NRT with the extended use in that data.

Combination therapy, where quitters use a long-acting transdermal patch as a baseline treatment and address individual breakthrough cravings with short-acting gum or lozenges has also gained widespread acceptance globally, as a safe and effective form of treatment.

The previous reference clinical practice guidelines for smoking cessation also recommended the potential of combination NRT therapy for highly dependent smokers. Using scientific support via published literature, pharmacokinetic data and experience in other markets, a more efficient approach

to expanding the role of NRT is quite possible.

When we consider in some areas 30 to 40 plus years of experience with these products, there must be and has to be valuable data to us all from that. Surrogate end points such as craving relief are also supportable for new products, where experience in other markets may not be available.

In conclusion, today's Part 15 hearing is a call to action in support of the FDA goals to provide new and effective treatment and solutions for current and future tobacco users. We all here today must find a fresh approach to keep pace with the changing face of tobacco and the population of users who want to find a path to sensation.

We at GSK Consumer believe our collective, renewed efforts in the area of medicinal nicotine can have a significant impact on the health of those tobacco users. This will help current smokers achieve what their ultimate goal is: sensation. Thank you.

DR. SHERMAN: Thank you for your remarks. Do we have questions from the panel?

DR. WINCHELL: If you're aware of some more

recently published studies that would support affirmatively recommending long-term use for all consumers, I hope you would submit those for the docket.

DR. KOCUN: Sure.

DR. WINCHELL: As we mentioned in the *Federal Register* notice, we've given considerable thought to what the data for long term use are, and we did feel that they supported removing the restriction against it, but not recommending it.

DR. KOCUN: Yeah, absolutely.

DR. WINCHELL: If there's new information on that, we'd be interested in seeing it.

DR. SHERMAN: Anyone else? I have a couple. Following on Dr. Winchell's question, there were a couple of places where you, I think, these were -- there were an evidence base to reduce to quit, temporary abstinence, combinations, use of NRT as needed and there were just a few we've been talking about. I notice you have references. But if there's additional evidence, we'd appreciate it.

DR. KOCUN: Absolutely, not a problem.

DR. SHERMAN: And then we'd really appreciate your thoughts on the optimal control and the optimal end point in the kinds of studies that you were discussing.

DR. KOCUN: Well, I think that's probably open to some consideration on a couple of points. So the first point would be the body of evidence that I hinted on Slide 9 of the extensive use of these products, okay. So what can we -- what can we align on and glean on from that data that exists today, and then what in addition to that would we need to add? So specifically, if you're looking for, you know, adding a different indication, that might require some additional data from a clinical trial-like setting.

But is it a craving relief end point versus a complete cessation? So I think to be specific, it would be first to align on the true value of all this data that sits out there, either in PROs or in consumer experiences or even patient experiences number one. We've seen potentially other health authorities really give that some weight, because they consider it real world use.

Sort of how a consumer uses a pack of cigarettes, for example, and how we can compare that to the products that we've had available there as well. Once that was aligned to, then I think the actual data can be determined of a clinical trial setting.

DR. SHERMAN: And one last FDA-ish question. When you said that a surrogate, craving as a surrogate, are you using that in the way we do a surrogate for a clinical benefit, implying that craving relief is not its own clinical benefit or were you using it in a different way?

DR. KOCUN: No. I was using it in a different way in which we I think have to determine what benefit that actually has, because I'm not sure that has been recognized at least in the past. I think there's becoming to be a recognition that there is slightly different but are 14 to 1, 1,400 to 1 in two conversations earlier today, right? Where is that benefit? But there is a benefit there.

DR. WINCHELL: Actually my question is related to that, which I interpreted your suggestion to use craving reduction as a surrogate end point to mean that

craving reduction in the context of a study would be used to, as a surrogate for success in quitting smoking.

DR. KOCUN: Yes.

DR. WINCHELL: Which is already a surrogate for clinical benefit. So we're interested in this. We've been interested in it for some time. The literature on measuring of craving, definition of craving, how people understand craving, how predictive craving is of future smoking is equivocal.

So if there's new information or a new lead developed and instruments are validated along the lines of our PRO guidance with benchmarks for clinical relevance or predictive changes, those are things we'd be interested in your submitting.

DR. KOCUN: Absolutely, okay. No problem.

DR. DRESLER: I am kind of building on the craving relief and using that as an indication, and going to a previous presentation too. So is there -- are you saying that there may not need to be an end point of cessation but concomitant use of some decreased number of cigarettes and NRT would have a

public health benefit or an individual benefit?

DR. KOCUN: I think in certain smokers, yes. All right. So I think what we would have to determine is whom that would be, number one, and then number two to what time frame are we discussing, and then to what extent is there going to be the individual public health benefit and then the overall public health benefit. So yes.

DR. DRESLER: So since you're a physician, I am going to push you on that. So and let's -- so for individual health, so what would be the benefit that you would be looking at for what duration of time that would be good for the individual to concomitantly use? So is that within a year that they concomitantly use, or is you're looking at putting something on the market that would help people with craving relief and/or do cessation? Is that a year or two?

DR. KOCUN: Yeah. I mean --

DR. DRESLER: How do you do those studies?

DR. KOCUN: Yeah, you know. We would have -- I would have take back and think that through a little bit of a hard time frame stop. You know, six months to

a year probably seems right for some. But I'd have to take that back and sort of think about through what that would be from a --

DR. DRESLER: So concomitant use before pushing for -- before pushing for the cessation?

DR. KOCUN: Yeah, yeah. And again, for probably a heavy smoker absolutely, right, and then probably have to think about modifying it for others.

MS. SIPES: So I want to follow up on that. I think what Dr. Dresler was talking about is a concomitant use of cigarettes and NRT has also been called dual use.

DR. KOCUN: Uh-huh.

MS. SIPES: So I just wanted to follow up on that. Are you -- just sort of thinking of scenarios, are you -- are you thinking of a therapeutic scenario where somebody would dual use for a certain period of time and then progress to cessation, and if so, how does that -- how does that intersect with your thoughts on the addictiveness of nicotine?

DR. KOCUN: Yeah. So I think just to be clear, when I was speaking about combination, it was

more a combination of multiple nicotine replacement therapy products than smoking and the NRT. However, we do know individuals do do both, right, smoke and take nicotine replacement. We, you know, spoke this morning about one to two cigarettes and so forth so --

MS. SIPES: Sorry, just to clarify. So when you were -- in your colloquy with Dr. Dresler, you were talking about combination use of different NRTs and not NRT plus smoking?

DR. KOCUN: Correct, yes.

MS. SIPES: Okay.

DR. SHERMAN: Go ahead.

DR. WINCHELL: I do have one additional question. You've referred to both the quitting smoking by gradual reduction and quitting smoking by combining two products as new indications. In our view, the indication for both of those would be quitting smoking, and I'm wondering if you have -- is there a particular strong reason that you would view those as indications, that that's an important word for you to use as opposed to treatment regimen?

DR. KOCUN: I'm not so sure we're held to the

word, but it's really more of what we can then communicate to a consumer, and sort of the guidance that falls around there. So if the control elements around things like claims and safety messages as well I think is what we're hoping to engage in and get a better understanding, moreso than maybe sort of a traditional Rx indication if you will, just to be clear.

DR. SHERMAN: Any other questions from the panel? And I thank all the presenters. We're going to take a 15 minute break and we'll resume promptly at 10:25.

(Whereupon, a short break was taken.)

DR. SHERMAN: Okay, we'd like to begin. Can everyone take their seats please? Just two comments. We heard there were some difficulties with the microphones from the panelists. Apparently, I'm the sensible deputy commissioner, so if someone could let Dr. Gottlieb know that, I'd appreciate it. But if it's not fixed, let us know.

The other thing is I apologize for not -- I usually practice the names ahead of time but it's post-

shutdown week, so I'm now up to speed on the names.

(Laughter.)

DR. SHERMAN: Our next speaker will be John McCarty. No? Oh no, I'm sorry. Dr. Charles Garner. No, I'm not up to speed yet. I still blame it on the shutdown.

(Laughter.)

Dr. Charles Garner

DR. GARNER: Thank you. Thank you, Dr. Sherman. You got my name right the second time, so that's good.

DR. SHERMAN: Thank you.

DR. GARNER: I'm going to be making some comments on product to process consideration for emerging NRT products, and I'm going to start with a couple of introductory points. RAI Group Companies are in alignment with the Agency. We believe this is an extremely important FDA initiative, and has the potential to expedite the path to market for novel and effective NRT products, and this will have a positive impact on public health.

RAI Group Companies are committed not only to

transforming tobacco with products that the FDA determines to warrant modified risk tobacco product marketing orders, for example we filed a Camel Snus MRTPA last year which was accepted for filing in December of 2017, but also developing NRTs to provide better and more effective options for smokers who want to quit, as will be discussed later.

Under Nicotivum and the Zonnic brand, we already market CDER-approved NRTs for smoking cessation. I'm going to start with three key principles. First and foremost is the simple fact that smokers moving off combustible products like cigarettes need a place to land.

They must be offered a variety of options of non-combustible sources of nicotine, and while current NRTs are effective, they still do not help the large majority of their users become smoke-free. We believe the path forward will involve a coordinated and a comprehensive approach that includes both medicines and tobacco products.

Secondly, relative risk misperceptions of nicotine and nicotine-containing products are a

significant barrier to trial and use. There needs to be a concerted effort to destigmatize nicotine and educate the public with respect to harm related to smoking versus the harm related to nicotine without smoke.

Industry alone cannot correct these misperceptions. Other voices need to weigh in. There must be an alignment of the message across government agencies and public health organizations. Thirdly, the focus of the approach needs to be the smoker. That means that the product not only has to deliver nicotine quickly and effectively, but the product must be appealing to adult tobacco consumers on many fronts, not just pharmacologically.

Equally important, our consumer research for Nicinovum has found that most smokers do not perceive themselves to be sick, and therefore may be reluctant to seek a medical solution or define themselves as having a chronic disorder. Communication strategies by public health authorities should reflect this reality, if they are to be more effective.

Now a bit of a more detailed discussion. As

part of our commitment to transforming tobacco, we are pursuing product development programs across a full range of tobacco and nicotine products. We believe that offering a wide array of products, some regulated as tobacco products and some as medicines, will best serve the most smokers as quickly as possible in their journey to quit smoking.

One key benefit we see of offering medicines is to provide reassurance to consumers and clinicians, who look to the FDA as an expert and unbiased arbiter of safety and efficacy. Since 2010 we've marketed three flavors of nicotine replacement therapy gum under the Zonnic brand name. Zonnic broke with many conventions that governed the NRT category until that time.

For example, we distribute Zonnic primarily in convenience stores and gas stations, where approximately 70 percent of the smokers buy their cigarettes. We offer a ten count pack that most retailers sell for substantially less than a pack of cigarettes.

In addition, the advertising is placed in

close proximity to cigarettes to intercept smokers while they are in the process of purchasing cigarettes. These innovations increase smokers' access to proven stop smoking products. In addition to the Zonnic gum, we have subsequently introduced the Zonnic mini-lozenge, which utilizes the same marketing and distribution strategy as Zonnic gum.

Furthermore, we have developed several other potential NRT products encompassing a range of product types, and we've discussed the regulatory approval requirements for this novel products with CDER on multiple occasions. While we've gained regulatory approval and are marketing some of these products in other geographies, for example the EU and Canada, we have yet to submit any of these to the FDA because of the pre-market requirements in the U.S.

The difference in marketing clearance process between the U.S. and other countries is primarily due to the fact that in the United States, the pre-market burdens we have faced and anticipate for future development of NRT products are substantial, both in resources and most importantly the length of time it

takes to get products to the market.

Now while vaper products are not formally NRTs, many studies have shown that they show significant promise in helping smokers either quit smoking or significantly reduce their cigarettes per day. Many smokers may be choosing vaper products because vaping is more than just nicotine replacement.

Smoking is a very complex behavior that involves not just nicotine pharmacokinetics, but also sensory cues and a learned complex behavior. As such, vaper products offer tremendous potential as an innovative class of NRTs.

We believe we have an opportunity to reassess CEDR's current approach, particularly in light of Commissioner Gottlieb's announcement in July 2017. A multi-year and multi-billion dollar development and regulatory program for each new NRT would both delay the availability of effective cessation products but also would discourage many sponsors from committing to such an arduous endeavor. We are keenly aware that the FDA has a responsibility for ensuring safe and efficacious NRTs are available for Americans want to

quit smoking.

But the success of an integrated approach by health care providers, public health and the MHRA in the United Kingdom has proven to be quite successful in providing smokers with both efficacious products and a consistent message. This should not be overlooked. The fundamental MHRA requirements for vapor NRTs can be simply described as a three-pronged approach.

Demonstrate sufficient quality in manufacturing and product, so a GMP approach; complete pre-market clinical work to demonstrate that the delivery of nicotine falls between that of existing NRTs and cigarettes; and the development and execution of a strong post-marketing surveillance program.

If the FDA wishes to streamline the regulatory approach for NRTs using the MHRA approach as a guideline, it might be a reasonable place to start. The key foundation to this approach is the fact that nicotine pharmacokinetics, pharmacodynamics, product use adverse effects and the overall toxicity safety profile are well understood and have been for many years.

Smokers will benefit if both modified risk tobacco products and novel and effective NRTs are developed and marketed. We look forward to working with the Agency on this important endeavor. Hopefully, our thoughts and ideas expressed in this testimony have been useful, and we will be following the efforts of the Nicotine Steering Committee with great interest. Thank you.

DR. SHERMAN: Thank you for your comments. Questions from the panel?

MS. CALLAHAN-LYON: So I just want to make sure I'm understanding, or maybe I'm reading into what you're saying. But it sounds like what you're proposing is kind of merging the modified risk tobacco product process with cessation and NRT process, so that people would have an option of going from smoking to a modified risk product to an NRT product to cessation. Is that more or less what you're thinking?

DR. GARNER: It's -- no.

MS. CALLAHAN-LYON: Okay, all right.

DR. GARNER: It's not. What I said was, and this is actually good, because on the panel we have

representation from both CDER and CTP.

But I think you guys need to talk and you guys need to look at the overall approach, which is having modified risk tobacco products on the market, the communication of a message that there is a differential risk of tobacco products, and then sort of an expedited way to get novel NRTs that have demonstrated that clearly are not NRTs like vaper products, but have been demonstrated to help people stop smoking through CDER in a more linear fashion.

DR. DRESLER: I wanted to go back to your comment that your smoking cessation products are aligned with cigarettes in the convenience stores. So I'm wondering where your company is on cessation versus dual use. You know, I've pushed the previous presenters on this similar question.

So when -- is it co-marketed together so that there really could be -- you know, when you can't smoke you can use the NRT product? Or is -- are you really pushing in those environments for cessation from your other products?

DR. GARNER: It's the latter, okay. So we

don't co-market cigarettes and NRT products. The label is pretty clear. But what we do is rather than selling it in a pharmacy, you know, in a large count, we sell them in a smaller content and we have our advertisement placed in gas and convenience stores, where people go and look and see their cigarettes.

So they will see our advertising next to the cigarette advertising, and that might be a trigger. It actually has been a trigger, because that is a -- that's a good place to sell it. Plus, they're in smaller count packs. So the outlay for the individual is less than the outlay to go to a pharmacy and buy a larger count pack.

DR. DRESLER: Do you have any post-marketing evidence on how well that's working for cessation from in -- marketed in that venue like that?

DR. GARNER: I don't have any with me right now, but I will check. We are planning on making comments by the 15th of February, so if we have any information, I'd be happy to provide that.

DR. DRESLER: Thank you.

MS. SIPES: Question following up on that.

Your first key principle says "Smokers moving off of combusted products like cigarettes need a place to land. They must be offered a variety of options for non-combustible sources of nicotine." So in terms of your thinking and your business strategy, is the end game cessation of smoking or cessation of nicotine use?

DR. GARNER: Well I think the end game is to kind of look at smokers. There are some smokers who -- there's what 40 million smokers in the U.S. Some of them don't want to quit. Some of them like using tobacco products but would move to a less risky tobacco product, and some do want to quit and we need to provide them novel and effective NRTs to give them an opportunity to reach that goal.

So what we're trying to do is try to provide products for smokers, those that want to continue to smoke and those that want to quit, and lower risk products for those smokers that are in between.

MS. SIPES: So for some portion of users, the place to land would be a permanent place to land?

DR. GARNER: I'm sorry?

MS. SIPES: The landing. You said they need a

place to land in the form of non-combustible sources of nicotine. So for some portion --

DR. GARNER: Smokers that want to quit smoking need either a reduced risk product that they can land on, or they need an NRT to help them land in the area of cessation.

DR. SHERMAN: Other questions from the panel? All right, thank you. Now it will be Mr. McCarty's turn.

(Pause.)

John McCarty

MR. McCARTY: Do I have to wait for the light?

DR. SHERMAN: No.

MR. McCARTY: Okay, good morning. Thank you very much for -- the FDA for providing this opportunity for me to discuss my nicotine product. I'm a pharmaceutical product development person and been doing it about 30 years, and I'm an entrepreneur. I've definitely been overpowered by the former species, to say the least.

So I will go through. I want to also provide an acknowledgment to NIDA that provided the funding for

the studies, these PK studies that I'll present some data on, and also especially Dr. Frank Vocci of Friends Research and also Dr. Jed Rose of Rose Research Institute Center, that I have -- we're collaborators on these grants and also, without their help, it would have been impossible for me to proceed.

I'm going to be addressing two questions. Question No. 1, which is also split up into two questions, might there be ways to improve upon current delivery systems to move an over-the-counter nicotine product that might be more effective, and then I'll address what evidence might be needed.

Essentially very few products have been approved over the last years, even though clinicians and scientists have been demanding a faster-acting product. Why? Because acute cravings can lead to relapse within ten minutes or less. Also, a rapid release NRT with faster onset of action such as within the first three minutes could forestall relapse and enhance clinical efficacy.

Going to a technology a little bit, this is a thermodynamically driven drug delivery system where the

drug resides, is a solution within a tablet, and it's when delivered sublingually or buccally it has a rapid onset of action and also increased oral bioavailability. This shows where the tablet is placed, and also this is a highly vascularized area, which helps in regards to the absorption of drugs through the oral mucosa.

This is a patented technology worldwide. Pharmacokinetics demonstrated rapid delivery and fast onset of action, with T_{max} typically occurring within 15 minutes. It's applicable to both water soluble and insoluble drugs, and it uses only GRAS-listed pharmaceutical grade USP monograph excipients. It also uses standard manufacturing equipment, which means cost of goods can be considerably, is very low.

Here is an animation to kind of explain the technology. As you can see here, in this case this is nicotine which is put in a vehicle of a fatty acid, maleic acid. This resides as a solution in a tablet. When water from the saliva enters the tablet, it breaks it up very rapidly, and it also provides the driving force for the nicotine oleic acid vehicle to go into

the mucosal membrane.

Essentially oil and water don't mix, and it's going to try to find an environment which is most applicable, which is an oily environment, which are the lipids in the oral mucosa, and from there it rapidly enters the capillaries for systemic delivery.

Some of the attributes of the nicotine product. We have a Tmax within 15 minutes versus typical 60 for the gum and other sublingual products and lozenge, and smoker's cravings are satisfied by the rapid rise in blood nicotine levels similar to smoking. It meets ICH requirements for two year stability. It's easy to use like a breath mint. It can be used anywhere cigarettes and vaping cannot, and it rapidly disintegrates upon administration.

It's safest with the nicotine delivery products on the risk continuum. It's essentially a nicotine replacement therapy. I should mention that it also does not cause irritation because when it's in -- nicotine is caustic as a free form as a base. When put into an oil environment, it essentially does not have its caustic attributes and we don't see any irritation.

Okay. It's also very low cost of goods to make it competitive with cigarettes. So what about NRT efficacy? Almost 30 years ago, Cynthia Pomerleau and Jed Rose, who were pioneers in smoking cessation, could find the necessary attributes of a good successful NRT as being the method is safe and easy to use, specific dosages should be accurate and reproducibly delivered, and most importantly the nicotine PK should resemble cigarette smoking as a sharp rise in plasma nicotine followed by decay is a pattern believed to be responsible for the unique reinforcing effects of smoking. IntraTab's nicotine product meets these criterias.

Here is a graph showing various pharmacokinetics from various products, and as you can see here, smoking is the one to the far left. I don't know if this -- here, this is cigarette smoking, and as you can see also, the one that does the closest job is the nasal spray, and then you have the various ones. Here's the patch. So the nasal spray matches more -- is close to meeting the Tmax, but definitely falls short on the Cmax.

This is a lot of data on this slide, but what I want to point out basically is the average quit rate and odds ratio versus T_{max} and C_{max} . T_{max} for a smoker, the time to getting nicotine and the amount of nicotine is what's important. This is what they're really looking for.

So as you can see the patch, the average quit rate is about 14 percent, and you go down. Most of the other ones, the inhalers, the sublingual tablet from J&J and the gums and lozenge are approximately in the same area. But what's interesting is nasal spray. Nasal spray has an average quit rate of almost double of that of the patch.

The problem with nasal spray is it's really rude to take. Taking pure nicotine or diluted nicotine in free form and putting it into a spray and putting it into your sinuses, you've got to be a real man to do that. Most people cannot take the irritation that comes from that. So that's why it's not been a very successful product.

And you can see the pharmacokinetics. The T_{max} is 11 to 18 minutes, and the C_{max} is about 5 to 8

nanograms per mil. Here's pharmacokinetics, about 1 milligram and 2 milligram product. The 1 milligram product is on market as Nicofi, which is a dissolvable tobacco product registered with Synar Tobacco Products, and the 2 milligram.

Notice here again a rapid rise in plasma levels at first point on the yellow curve. For the 2 milligram it's four minutes, the second one's eight minutes. So you're seeing within ten minutes we're reaching plasma levels comparable to a cigarette. The other thing to note here is the dose proportionate delivery. The 1 milligram comes up to about 4-1/2 nanograms per mil, and the 2 milligram comes up to about 9.

We are conducting a 4 milligram study. We haven't got the pharmacokinetic data yet. We do have the craving data, and we anticipate we'll be somewhere in the range of 15 to 20 nanograms per mil, which is comparable to a cigarette.

Here is a table with various nicotine products compared to a cigarette, and as you can see cigarette Tmax between 5 and 8; Cmax between 15 and 30. Our

product, and this was a study with NIDA with six subjects. You'll notice the Tmax here is 17, which is a little further down the line than it was for the other one. That was a single subject.

There was one subject in this study that swallowed the tablet, which actually skewed the statistics to push the Tmax out. The reason we know this, the plasma profile was bad and he also complained about having an upset stomach. You swallow nicotine you're going to have an upset stomach. The Cmax is about 7.7 for the 2 milligram.

You come on down and you can see the various other ones. The one I want to point out MicroTab by J&J. It's also a sublingual tablet, but its Tmax is 60 minutes. It's a -- it uses the free form of nicotine, but it uses it in a cyclodextrin complex, and the Cmax is 3.8. So as you can see, our delivery system provide almost double the Cmax and five, four times faster delivery.

So this is a true indication that the technology is very effective in delivering rapidly and getting high bioavailability. It's almost twice the

bioavailability of a comparable sublingual tablet.

Here is the craving data for the 4 milligram, and this is -- the top area is the 4 milligram lozenge, and the bottom one is our sublingual tablet. The rate between 1 and 3 minutes is about twice as fast, and as you can see, the cravings went from basically almost halved in the first three minutes.

This we think is very, very important. We were very pleased to see this. This is in 24 subjects. The study was not powered. The power was about .53. So we really weren't anticipating to see a difference, but we obviously did and this was very encouraging.

All right. What evidence would be needed to support such a change? Obviously, this goes along the NRT route. We would be needing to do single and multiple dose pharmacokinetic studies, a craving or withdrawal study, and an OTC label comprehension study. My pitch here is I don't think there's a need for smoking efficacy studies, cessation efficacy studies.

Why? Because NRTs are well-established therapies for smoking cessation. It is very expensive, costing over \$10 million and it typically takes over

two years to complete due to a large number of subjects needed and a protracted enrollment period and a follow-up assessment. This really delays the introduction of novel NRTs into the market, and hopefully the FDA will consider alternative indications rather than smoking cessation as an indication for approval of new novel NRTs.

What evidence would be needed? This is a list of currently used, very useful craving and withdrawal questionnaires that have been standardized and used throughout the industry to determine either cravings or withdrawal.

Question No. 2. Are there additional indications regimens for OTC nicotine products that could be explored, and what evidence would be needed? Basically, craving and withdrawal are indications of suffering and discomfort needing therapy. It's much like having a headache or some other thing like that, where we go -- we provide aspirin or acetaminophen to counter out, to counter effect suffering and discomfort.

Several studies have concluded that craving hinders successful smoking cessation. It's also

associated with relapse in periods -- after periods of abstinence. Products should be able to be approved based on either of these stand-alone indications.

Evidence to support craving study is done by GSK. GSK got a craving indication for their 4 milligram strength mini-lozenge in a placebo-controlled study with 323 patients, half on placebo, half on the 4 milligram and this was done with a five question questionnaire on cravings. The primary outcome measure was at five minutes, with secondary measures at 1, 3, 7 and 10. A similar study design could be used for withdrawal.

In conclusion, very few NRT products have been approved in the last decade and little has changed to enhance their efficacy. Part of this is because of the cost and time in order to get a new NRT approved. FDA is open to innovative approaches and alternative claims to obtain market approval of new NRTs. That's the reason we're here today.

And IntraTab has developed a novel nicotine sublingual tablet with fast onset of action. Fulfills the lowest harm in the risk continuum, and the rapid

rise in nicotine plasma levels helps satisfy craving. Craving and withdrawal are indications of suffering and discomfort, and hinder successful smoking cessation and associated with relapse and periods of abstinence. With that, I will open the floor to questions from the panel. Thank you.

DR. SHERMAN: Thank you for your comments.

Questions?

DR. DRESLER: I think I'm training everybody if I don't have a question, so yes, I do. So you had - - you had two studies that I saw. One was an N of 24, one was a N of 6. In the N of 6, somebody swallowed it, and so he had an upset stomach. And then earlier you alluded to the nasal spray, how unpleasant that is. So rapidly delivering nicotine to the oral mucosa and/or pharynx/larynx is also pretty irritating.

So I'm wondering what sort of -- you were talking about efficacy, but I didn't hear any safety or adverse events from that very rapid delivery of nicotine to the oral.

MR. McCARTY: In the 24 patient study with 4 milligram, we had no adverse events, okay. Now then as

regards to irritation, the oleic acid we don't see any irritation. We haven't seen that --

DR. DRESLER: No, from the nicotine. The irritation and the burning, it usually causes a fair amount of burning and irritation.

MR. McCARTY: Or the tingle or whatever?

DR. DRESLER: Correct.

MR. McCARTY: That is an attribute of nicotine.

DR. DRESLER: Correct.

MR. McCARTY: And there is no way of getting around that, and quite honestly smokers like that. It's like a cue, like a Pavlovian cue that burn or gives them the feeling that they're getting the drug and the rush.

When we first looked at putting Nicofi out, we asked some smokers about that, and they actually preferred the fact that it does have a slight burn and it's going to be very hard to get around that problem because it's an attribute of the molecule itself. However, burying it in oil does cut down on the amount of irritation so --

DR. DRESLER: I wonder if there's a dose limit that you can have for that, because you're talking about upping the dose with the more rapid delivery, and I'm just wondering if you're -- but anyway, that was one thing. The next thing is that I'm thinking of an article that came out in the *JNCI* in January, that talked about the importance in a longitudinal study of using behavioral intervention for cessation.

So I'm wondering and they were calling into question the efficacy of the cessation products without behavioral intervention. I'm wondering if you're -- that's another attribute of those smoking cessation trials. They usually have some behavioral interventions, and I'm wondering if you're thinking that that would be important for your product also?

MR. McCARTY: I think behavioral intervention would be helpful with anybody trying to get off an addictive syndrome of any type. However, many smokers never go that way when they go onto NRTs without ever having any behavioral intervention, and I think a lot of people can actually quit smoking. My father was an example. He was in the hospital for two weeks, been

smoking for 30 years and since he had a two week lapse period, he never went back to smoking. He went cold turkey.

Not too many people do that. I think that's unusual. But so I think there's a place for it, but I'm not sure that all the population requires behavioral intervention. If somebody really wants to quit smoking, I think that motivation is probably more important than the behavioral support. But that's just my opinion.

MS. CALLAHAN-LYON: Just out curiosity, how long does this product last in terms of efficacy? You administer it and you have a very short time of action. But does it -- is it administered similar to other NRTs? Do they have to take them more often? What is your expectation?

MR. McCARTY: That's something we would find out in a multiple dose study. In fact, I think we would probably do it as an adaptive design instead of doing you're going to take it every 30 minutes or every hour. The MicroTab, the sublingual tablet that's sold in Europe, it's not approved here in the U.S., they go

for about 20 to 24 tablets a day.

So they're administering about every 30 minutes to an hour. The thing about smokers is a smoker will figure it out. They know how to dose titrate probably better than anybody on the planet. They will understand what they need to do and how often they need to take it, to take care of their desire for nicotine.

DR. DRESLER: So if I can follow up with that, because I agree with you. You can put all the instructions you want on the box and we all do what we want.

MR. McCARTY: Uh-huh.

DR. DRESLER: I should be careful saying that, I suppose.

(Laughter.)

DR. DRESLER: But you know, so you have to give instructions for the people for guidance for how to use, right?

MR. McCARTY: Right.

DR. DRESLER: So then and that was another thing too, because if I'm hearing your suggestion, is

is that NRT works. We know that NRT works. But they do have instructions for how to use it, and we also know that the more you use the NRT, particularly on a program, the higher your quit rate is. So then I'm wondering this goes to your multiple dose study that you're talking about, but then adherence to that multiple dose is really important for the efficacy of the product.

And so am I hearing you say yeah, the single dose or multiple dose studies, good enough and then we really don't need to tell the user how to use it?

MR. McCARTY: No. I think we would -- we would match from the multiple dose study. We would have a dosing regimen which would be useful, and I think that's why if it was done with an adaptive design, we might have a range of which the product could be used at, or we could do the standard protocol, which is take it every 60 minutes and just measure their plasma profiles along those lines.

I think we will obviously have to have something on the label in regards to a dosing regimen, but and that could be following along the same lines as

MicroTab, which is like I said 20 tablets a day.

DR. SHERMAN: Ms. Stewart, do you have a question? Your light's on?

MS. STEWART: I do. I think that craving is often characterized as one type of withdrawal symptom, but you seem to indicate that craving and withdrawal could be separate stand-alone indications. Can you say a little bit more about that?

MR. McCARTY: There are two different -- there's a withdrawal scale and there's a craving scale. Now I have to admit in some respects, they're very similar and it may be difficult to distinguish that. But if you're using a craving scale, then I would say that you're going for a craving indication.

If you use the withdrawal scale, you're going to for a withdrawal indication. Quite honestly, these could probably be combined and in which case you could get an indication for both withdrawal symptoms and craving symptoms.

DR. SHERMAN: Can I quickly follow up? So then I'm not quite following, because you had stated that MIT's well established for smoking cessation. So

what would be the comparator or the end point? Is it about equivalence or is it a PRO measuring craving?

MR. McCARTY: Our reference listed drug would be the lozenge.

DR. SHERMAN: Okay, thank you. Any questions?

DR. WINCHELL: I have a question. I'm looking at your Slide 14, your craving study, and if you have some details on the scale that you used and how it -- how you interpret this, whether reducing people's craving scores to 20 is predictive of them being able to refrain from smoking, what numbers you have to achieve, that would be very helpful information for us to have.

MR. McCARTY: This was a pilot PK study, and quite honestly the craving was done as a secondary indication or a secondary end point. The power on this study was .53, as I think as I had mentioned. So we really weren't expecting much in regards to that. The P value on here was .16, all right. So I think that that would have to be addressed in a larger study.

DR. WINCHELL: Right. But even before pursuing a larger study, we would like to have a better

understanding of the instrument, and how to interpret the results of the instrument. So if you've got some information --

MR. McCARTY: Well this was done on a standard -- this was done on a standard five question craving.

DR. WINCHELL: I'm just asking if -- I know there are many, many scales out there. Many people use them. We need additional information on how to interpret the results, and whether there's some amount of reduction or target score that is -- translates to people not smoking. So I'm just asking for that.

DR. SHERMAN: I think we're going to take this offline and go on to the next speaker. Thank you.

MR. McCARTY: Thank you very much.

DR. SHERMAN: The next speaker is Matthew Myers.

Matthew Myers

MR. MYERS: Thank you, and I think from my talk is a little bit different. First, I want to thank the Committee. I want to thank Commissioner Gottlieb for creating the Committee, because the one common theme that we've seen is that there is a uniform view,

that there really is a need for a significant review of how FDA is reviewing nicotine replacement therapy.

We come together at a unique time for multiple reasons, and the question is really going to be whether we seize that opportunity. We've had hearings before where we've discussed these issues, and not much has changed. I think the fundamental question this time is are we -- is this going to be different? Are we going to do something different as a result of this initiative?

We come together at a unique time for three core reasons. First, Dr. Gottlieb's proposal is bold, but it will only succeed if all three components are done in an integrated form. His recommendation of reducing nicotine in cigarettes down to minimally addictive levels offers extraordinary opportunities, and for the purpose of the initiative we're talking about today, it both creates an incentive for manufacturers to want to engage in product development, because there will be a market out there.

Second, if done right, it ought to reduce many of the downsides that most of us fear, which is that

the development of certain products will simply lead to long-term dual use of cigarettes and extraordinary uptake by young people. Done together, this opportunity really comes together.

But it needs to be done together, and too many people already today have put a silo without being critical, but probably being critical. You know, Reynolds talks about its Zonnic, but it doesn't talk about it as its marketing of menthol cigarettes to vulnerable people throughout the country. We need to drive down the use of cigarettes at the same time we're making products available.

Second, prior to 2009 CDER was the only FDA center with authority to do something about the tobacco problem and nicotine. Today, we come together at a time where FDA has jurisdiction over all forms of nicotine, no matter how delivered. That should alter how the discussion takes place.

The last two days we spent in the hearing with a product created by Phillip Morris International, which it claimed would quote "reduce harm and assist many smokers to switch." Didn't answer the question,

the fundamental question that was asked earlier today here, which was were we switching these people long term forever to this product, or was our goal to end the use of nicotine.

I want to answer that question today, but FDA has the opportunity to say what are its goals as it moves forward here? Yesterday's hearing demonstrated something very important. There is a market out there that is large enough to prompt major manufacturers to spend the money to produce high quality products if the pathway that FDA offers is one that is open and makes sense.

This is a problem we could solve, and it's absolutely essentially to do so. Yesterday's hearing demonstrates that. But at no point yesterday did we actually talk about the goal of cessation. It didn't come up once in the discussion. These conversations can't take place in silos.

Three, the fundamental dynamic of the marketplace today is totally and completely different than when many of the rules were promulgated that were looked at. This reality is nicotine is available to

literally any consumer anyplace in this country who walks into a shop and is capable of inhaling it. What we haven't done is created a set of rules and regulations designed to drive that market as much as humanly possible to the place where its public health goals are paramount and clear-cut, and our priorities are clear cut.

So I have a number of specific recommendations, but before I get to them, the very first things I think I want to say is the outcome of this hearing is going to be measurable from our point of view, and that is whether action is taking place. There's some very concrete things. This is a great first step.

It requires CDER and FDA to be bold. It requires -- I would urge that today should be the first of a set of hearings where FDA brings in manufacturers across a broad spectrum, after having set clear cut goals about what its public health initiative is, and say what do we need to do to create a pathway that will provide you incentive to move forward on the development of innovative products that will actually

save lives.

To do that, and this is the next critical point, it requires coordination. The value of this Committee today is that it includes the Commissioner's office, CTP and CDER. This will not be solved operating in silos. Commissioner Gottlieb talked about a continuum. Continuum isn't three separate silos, one for cigarettes, one for MRTP and one for drugs that help people quit. It is designed with clear cut goals and moves down there.

I would urge as well that the FDA make very clear that its number one priority is total cessation. That's where it should be moving from. We should only then talk about the need for products for longer term use within the context of driving down cigarette use and is a long-term pathway to quitting with regard to that.

There's a third component about it which also requires careful thought, and that is if FDA allows the sale of nicotine-based products, vaper products, e-cigarettes etcetera, without requiring as a minimum standard evidence that those products actually assist

people to quit or to switch completely, then all we're doing is creating a new marketplace for recreational nicotine, which will sustain ourselves and probably the tobacco problem for decades going forward.

I mean you've already heard the real issue here, which is we have a crisis. We have made extraordinary progress in this country reducing tobacco use, but almost all of it has been in the prevention criteria. We have only made modest steps forward in actually helping the millions of smokers quit. We know that 70 percent of smokers say they want to quit.

Our experience with e-cigarettes in adults demonstrates that you provide them anything that tells them there's a possibility out there, they're going to do it. It's our job to make sure that those people have the best available products, easily accessible, to do so.

In many respects today, our system is about as upside down as it can conceivably be. You can make a banana-flavored e-cigarette, bring it to market, sell it to anybody who's old enough to give you, to flash an ID, whether it's fake or not to be perfectly honestly

with you, with no evidence that it delivers nicotine in a way that's effective to quit, with no evidence that it's being sold to a smoker, and you don't need any approval of any kind that's effective at all.

You want to bring a product to market that has evidence of effective use of nicotine, you have to go through all of the steps. The answer isn't to eliminate good safety requirements.

The answer is to build a continuum that looks at both process, procedures and requirements, to make it the easiest to bring to market products that will actually eliminate the use of nicotine all together, to make the next criteria be one of products that could be a pathway to quitting, even if it is longer use of nicotine, and the greatest barriers to products that are simply being used for recreational purposes that have widespread appeal to use.

It's really this Committee's opportunity to set a set of rules to accomplish those goals. That won't happen if CTP operates in isolation from CDER, and the concept of a continuum isn't taken seriously as it relates to these kinds of issues. There's a sense

of urgency to this. We've had hearings before. The 2009 Act had a provision that said let's look at these issues.

There was a hearing held now almost six years ago. Nothing meaningful changed. A series of petitions were filed. There were label changes that were made. They were meaningful and they were useful. They were modest. We need something that is much more than modest today if we're going to succeed with regard to that.

Several questions have been asked about the right comparator, and I think that is fundamentally important when we look at this. You know, in critical respect our organization looks at one issue. How many people are dying from tobacco use? The right comparator is in the United States today 480,000 Americans are dying from tobacco use. The vast majority of them use a product that kills one out of two long term users.

We know that we have ways to protect young people from products that are well regulated. What we don't have is products that are sufficient to get a

vast majority of those smokers off of this product. If we were talking about a cure for lung cancer, we would be willing to take extraordinary steps to figure out how we motivate people to produce the product; how we deliver the product that minimizes harm, recognizing that zero harm may not be the right standard.

With through post-market surveillance and activities, actually take steps to minimize harm, and in the end create a sense of urgency. Well the reality is with 480,000 Americans dying every year, 36-1/2 million Americans addicted, if we could stop an additional million people a year from smoking, think how many lives we could save?

But that will only happen with a coordinated, aggressive approach, an outreach done by the Agency that isn't just passively waiting, sitting back here looking to this. We know a great deal about the health, relative health harms of nicotine. We don't know everything. We know a great deal about abuse potential.

But right now, what we have is the worse form. We have nicotine being sold to anybody who can purchase

it over the Internet and in virtually any store whatsoever with any set of flavors with regard to no matter who they appeal, without any scientific evidence on a population basis that those flavors are necessary to help people quit.

We should bring science to the whole thing and set clear priorities in doing that as we move forward. So I'm going to apologize. I'm not presenting you data. What I am saying, however, is that I think we have, as a result of Commissioner Gottlieb's proposal, a once in a lifetime opportunity. This hearing is a good first start.

But if after this hearing we simply go on to business as usual, we will have failed. So I think from our point of view what we're asking is pretty clear cut. One is FDA, get out of its silos, bring people together and say what are the right ways to provide a pathway and incentive to produce products that will, to the maximum extent possible, eliminate the use of nicotine altogether in any addiction.

Second, are there things we need to do in the interim as a pathway to that, given the MRTTP law so

that we're both complying with the law and setting clear-cut priorities. Three, take strong steps to create the greatest barriers for those products that are currently delivering nicotine with no evidence whatsoever that those products actually help people quit or switch, and with very high youth usage potential.

We may not know, as the National Academy of Sciences report said, whether or not these kids are going on to long term use. But we do know they are experimenting with these products in very large numbers. We shouldn't find ourselves ten years out in discovering we haven't taken the steps that we need to take in order to make this happen.

So our purpose of coming today really is to say we in the public health community, those who work on tobacco-related issues, are here to support you in every way we can. But what we're hoping is is that the challenge that Dr. Gottlieb has delivered in a three-prong approach, drive down cigarette use maximum, change how we're doing this, prioritizes total cessation and figures out how we clear a pathway to

make it a reality. Thank you.

DR. SHERMAN: Thank you for your comments.

Any clarifying questions from the panel? Ms. Sipes.

MS. SIPES: In your materials, you acknowledge that there may be some smokers who can't quit, in other words, who can't beat their addiction but who might be encouraged to switch completely, for example, to another type of nicotine-containing product.

MR. MYERS: Uh-huh.

MS. SIPES: I'm just curious. Do you think that the number of smokers who fall into that can't quit but would need to switch category, do you think that's kind of a fixed number, or do you think the number of smokers who fall into that category might depend on other factors like what other products are available or other factors?

MR. MYERS: I can only give you a non-scientific answer. Having watched this movement over years and watching this movement across different countries, it is absolutely not a fixed number. What we have learned is through the proper efforts to drive down tobacco use, change the social norms of tobacco

use, change where people smoke and change the price of tobacco products, that we have gotten populations to quit altogether that no one ever thought we would have succeeded in doing that.

As FDA sets its priorities, what we would urge is for this to be an ongoing reevaluation, with first step one clearing the pathway for total cessation. Step 2, as Dr. Gottlieb's proposal to reduce nicotine is implementing, ensure that there are adequate products to assist people to make that transition. But even in doing that, doing that, the goal ultimately needs to be long-term total cessation.

There may be a subset of population out there that will need it for some undefined period of time, and if the alternative to that is cigarette smoking, that's a trade-off that's well worth having. But we should never lose sight of the fact that our ultimate goal should be to reduce that number to the minimum absolutely possible.

DR. SHERMAN: Any additional clarifying questions?

(No response.)

DR. SHERMAN: Thank you for your comments.

Our next speaker is David Spangler.

David Spangler

MR. SPANGLER: I'm David Spangler with the Consumer Healthcare Products Association. We represent manufacturers of over-the-counter or OTC medicines, and those include OTC nicotine replacement therapy or NRT. So on behalf of OTC NRT makers, we welcome this opportunity to talk about helping more smokers quit.

You outlined a number of questions in your hearing notice. I'm going to focus on four areas. First, some general themes. Second, I'm going to talk a little bit about your Question 2 on additional indications or regimens. Third, a process suggestion that wasn't in your hearing notice, and fourth and finally, some aspects of Question 3 on data to demonstrate public health benefits, a reduction in consumption of combustible tobacco.

So first, some themes. The very fact you're holding this hearing is an acknowledgment of the power of access. We've heard about how access from a number of the speakers already has helped people reduce their

consumption of combustibles. For the past 20 years, having products to stop smoking at least as accessible as those that create nicotine addiction has a demonstrated public health gain.

For instance, OTC NRT availability led to over 400,000 quit attempts a year, an 150 percent in quit attempts in the first year of the switch from prescription to non-prescription status of NRT. Quitting smoking provides the greatest personal and public health benefit, but it's evident that smokers or more broadly tobacco users aren't all the same. That path to quit can be shorter or longer; it can be one of abstinence or relapse with multiple attempts; it may be one of limiting exposure including steps.

The very fact that the average smoker takes five to seven times quit attempts before success simply underscores how complex a path can be. But quitting should remain the objective. Indications that link to harm reduction or positive steps, but as the UK's Medicines and Health Care Products regulatory agency concluded, approving a medicinal product with only a harm reduction indication is not acceptable.

Let's talk about Question 2, indications or regimens. We agree that additional indications or regimens for OTC NRT products should be explored. A number of the examples you list in the hearing notice, things like craving reduction, relapsed, reduce to quit, cessation of non-cigarette tobacco products, all these claims or as the parlance of the drug facts label "uses," all these are tied to the path to quitting.

But we stress this path to quitting in combination with thinking about tobacco addiction as a chronic condition for many smokers. Preventing the chronic condition for many of these smokers has already failed. So how do we (a) arrest progression and (b), reverse it.

First, arresting progression. Where logic and literature support a claim, sponsors should be able to submit streamlined data packages for these supplemental claims. In your modified risk tobacco product application rule, you state "It is not necessary for epidemiological studies used to support a modified risk tobacco product application to focus solely on each specific uniquely identified product that is the

subject of the application.

We think a similar approach can be extended to OTC/NRT. Post approval epidemiologic studies or data might or might not be product-specific or small scale. Post-approval studies can further support such claims.

Second, reversing the condition of tobacco addiction. Remembering that quitting is the goal, are we on that path with supplemental claims? A published UK survey-based study found two claims on a potential path to quitting, smoking reduction or temporary abstinence with NRT were in fact predictive of quit attempts and abstinence six months later.

We acknowledge that such an approach, this literature and logic approach is without risk, and that of course needs to be monitored and in turn addressed, including nicotine use by a group that would otherwise be less likely to smoke, that's the most obvious risk of claims short of quitting that are too attractive.

One pre-approval means to mitigate risk is to continue to urge NRT sponsors to conduct label comprehension studies on their claims. If FDA pursues a path of literature and epidemiological data that may

not be product specific, we would of course expect FDA to continue to require a full quality module and a full safety module.

In a lot of instances, that would have been done with the four applications, since in many instances we would expect these to be supplemental claims.

Next, a process suggestions, not from your hearing notice. You've obviously in the Center for Tobacco Products built up a tremendous amount of expertise. For instance, you've developed expertise in understanding specific characteristics of products, how the specific characteristic and people's attitudes, their beliefs, perceptions, their use of the products.

Your scientists are working to understand the effect of different levels of nicotine and other factors in addiction. That's in the Tobacco Center. That type of expertise is precisely on point for the questions in the hearing notice. So why not tap more directly into that expertise in a new drug application review?

We suggest FDA explore having a Center for

Tobacco Product designee be a part of a smoking cessation new drug application review still under the lead of the Center for Drug Evaluation and Research. This could be a way to operationalize your commitment to a comprehensive approach to nicotine regulation.

Your Question 3, did it demonstrate public health benefits or reduction in consumption? You've heard from a number of speakers today with evidence on this question, and we will include further information on this in our written submission due next month. But preliminarily, just three supporting data points.

First, new studies in Sweden suggest reduced risks of lung cancer or chronic obstructive pulmonary disease, but continued risk with several other forms of cancer. I'd note these speak to Snus versus smoking, not dual use. Second, the UK's National Institute for Health and Care Excellence notes that there are no circumstances where it is safer to smoke than to use medicinal nicotine, and a lifetime use of NRT will be considerably less harmful than smoking.

Third, researchers in South Korea concluded that there was a risk reduction in reduced smoking, but

the size of the risk reduction was disproportionately smaller than expected from the reduced cigarette consumption. Those authors went on to suggest "Cessation remained the cornerstone of preventing smoking-related cancers, but smoking reduction could be considered as a strategy to supplement smoking cessation."

That conclusion is precisely why you've invited many of us to present to you today. We thank you for the opportunity, and we want to do our part in making tobacco-related death and disease part of America's past.

DR. SHERMAN: Thank you for your comments. Are there any clarifying questions from the panel?

MS. SIPES: So your firm representing OTC products is -- do you envision then the electronic cigarettes? We heard earlier from the electronic cigarettes. Would those be OTC products?

DR. SPANGLER: Today? No.

MS. SIPES: Oh no. I'm wondering what your proposal is or your recommendation or your thought would be?

DR. SPANGLER: That would -- that would be up to a sponsor to show that that met CDER's requirements. I think we would say we are neutral as to what the delivery form is. But I represent medicines.

MS. SIPES: So you're talking about just the current NRT delivery systems?

DR. SPANGLER: No, I didn't say that. I said we would be neutral on what any given sponsor would put forward that would meet CDER's criteria.

MS. SIPES: Okay.

DR. SHERMAN: Other clarifying questions?

DR. WINCHELL: I just want to make a clarification. You referred to the MRTP rule. It is not a rule. It is a draft guidance.

DR. SPANGLER: I stand corrected.

DR. SHERMAN: Any other clarifying questions?

(No response.)

MS. CALLAHAN-LYON: I have one. I might have missed it, but when you talk about this core application that other sponsors can reference, who's the application holder for that core application?

DR. SPANGLER: I was speaking of supplemental

claims, and I was simply suggesting, as in the draft guidance on Modified Risk Tobacco Products, that the support from epidemiology and literature need not to be product-specific.

MS. CALLAHAN-LYON: In the evaluation of a particular application --

DR. SPANGLER: That is correct, that is correct.

MS. CALLAHAN-LYON: Thank you for that.

DR. SHERMAN: Any other questions? Then we would encourage you, if you don't mind, to submit both your statement and all supporting evidence into the docket. Thank you for your comments. Our next speaker is Jeff Stier.

Jeff Stier

MR. STIER: Good morning. I'm -- that's not mine.

(Pause.)

MR. STIER: Well, I know my name so -- I'm Jeff Stier. I'm a senior fellow at the Consumer Choice Center, and if you're interested by anything I've said today, you can follow me on Twitter at jeffastier for

ongoing commentary on these issues. My presentation was also affected to some degree by the shutdown, the shutdown of the printer at my hotel last night, so excuse my form.

I'm intensely gratified that we have all come together today to have this conversation, and I'm grateful to be here to learn from all of the participants, and I appreciate the opportunity to share my thoughts and to receive feedback as part of this very important ongoing conversation. How wonderful is it that you've brought together companies, regulators, pharmaceutical companies, traditional tobacco companies, e-cigarette companies, trade groups, public health groups, consumer public health groups like mine, who are interested in advancing public health and advancing consumer choice from our perspective at the same time.

I do see this as a start point in time, not only because I agree with what much of what Matt Myer said today, which doesn't always happen from a consumer choice group. But I think that's important, specifically with the conversation about silos and in

the context of post-July 28th world we're in.

I thought those are very important points, and I want to kind of run through a whole range of topics. I don't think -- the title of my talk made up onto the slide, which is disappointing because that was the best part of it. NRTs in a class by itself. Do the ENDS justify the means? I figured it would take a second.

So NRT in a class by itself goes back to that issue of silos. I think we have the same goal, to protect public health, to deal with the -- as the FDA has said, is to deal with the harm from tobacco. But there are different pathways to market for different products that are falling in different classes, and there are different sets of rules.

Some of those rules are clear. Some of them are not so clear, and it's important that those rules will be clarified I hope with standards on the ENDS side of things. But it doesn't make much sense for -- and I'm asking this question. It doesn't make sense to have these silos, to have these different sets of rules for different products.

If they're all trying to do the -- ultimately

to protect public health, to help consumers, and certainly there will be different ways we have of getting there and different perspectives on say the role of long-term use of recreational nicotine and whether that's the real long-term target, or is it just protecting public health, where I think the FDA's goal is really properly focused on the real target, which is the harm that we have unfortunately seen from the role of combustible tobacco.

I think a lot about this environment, this regulatory system that we find ourselves in, and to me it's clear that -- and this hearing is evidence of that, that the Agency is doing the best it can with the authority given to it by Congress, with this system that exists now. But I wonder, and I'm not making a recommendation per se, because I know that will be one of the follow-up questions.

But I want to put the idea out there that is this the best system or is it an anachronism? Is it a patchwork of regulatory authorities passed at different times, that aren't now organized in a way that sets up the Agency to succeed, to maximize public health? Some

of the topics that we've been talking about this morning I think are so important.

The connection between satisfaction and addiction, and we saw the David Abrams, et al. slide that Dr. Graham shared with us, and I think that's so important to keep that in mind, the idea of satisfaction and the role satisfaction plays. You know, you have to ask yourself would we rather see if in the ideal world, we want to live in a world where nobody's ever using nicotine? Do we want to live in a world where nobody's using caffeine, long term addiction?

These are I think fundamental questions that will drive where we go from a regulatory standpoint, and I don't know that we want to target long term use of nicotine for certain adult users, if it will help guarantee that fewer people will die from the use of combustible cigarettes. So I question whether that's the right target.

The target I think that we should come together on, as the FDA stated, is disease and death caused by combustible tobacco, and then do everything

we can to lower other negative outcomes along the way. But I represent consumers. We believe in the consumer choice. We've learned a lot about the dangers of prohibition and the unintended consequences of that.

So I think we should be mindful of them.

Also, I want to talk a little bit about the unintended consequences and the need for good guidance for consumers. I personally was surprised to hear, maybe I misunderstood it, that there seemed to be a lack of clarity, that there's a beneficial health outcome from someone who reduces their cigarette smoking from was it 14,000, what was the number, to one, whatever that may be.

I think maybe I misheard it, that there's any doubt that dramatically reducing the number of cigarettes you smoke is a beneficial outcome. I don't have a study to share with you, but I'd be shocked to hear that everything I've heard is each additional cigarette that you smoke causes more harm, and my logical skills suggest to me that every one fewer cigarettes you smoke will do some good, especially if you get down to really, really low levels.

So I'm not an advocate for dual use, and I think it would be great if no one ever smoked any cigarettes again and didn't do themselves any harm. But the guidance that consumers hear when you put that information out into the real world, I'm concerned that there are people watching this today at home, consumers who maybe have been working hard to cut the number of cigarettes they smoke in half and say you know, I'm never going to get down to zero, and I've been suffering by cutting my smoking in half because I was -- and I was planning on cutting it in half again.

I just heard from the FDA there's no evidence that helps, and they're going to go back up, and what are the unintended consequences of lack of clarity from that advice, if that is in fact what people hearing out there? Is there an ideal level? We talked about the matrix and the sweet spot.

Is there an ideal level, or is it possible that individuals are different and have different considerations and circumstances, and as such there's no general -- there's no generalized sweet spot, that we need to provide consumers a range of choices along

that risk continuum that are appropriate for them?

I think those are important questions to ask. What are the costs of failed attempts? I think there has been a -- I think there needs to be, as part of this conversation, as part of this civil conversation, bringing so many different stakeholders together, which I think is like the first step Director Zeller has talked about, the need for us to come together and have that conversation about nicotine. That's why I'm so thrilled about this taking place.

But as part of that conversation, I think there's a little bit of responsibility on everyone here, and I would ask what is the obligation? What is the role of being slow to approve or encourage the introduction of more NRT that satisfies more people and that may be used over the long term safely?

As FDA I think maybe is recognizing implicitly that it needs to do better, and Dr. Gottlieb and Director Zeller have written about that in the *New England Journal of Medicine*, that we need to do a better job to protect American consumers.

So the cost of failed attempts. How many

chances do we get to help someone quit? Ideally it makes sense to start them off at the lowest end of the risk continuum, and only point them to higher risk products on that continuum as is necessary

. But in the real world, what if they are only willing to make three attempts, five attempts or a finite number of attempts and then they become disheartened and they're less likely to make another attempt?

What about the risk of medicalizing nicotine? Look at the enthusiasm for e-cigarettes, not medicalized? They give consumers a sense of control. Yes, it's enjoyable. I know that's sometimes a naughty word in public health.

But I'd rather see more people enjoying themselves and not killing themselves in the real world, and I think those are issues that the Agency, that the public health community, that the pharmaceutical companies and the tobacco companies, everyone needs to think about those issues.

That's why again I'm so gratified that we're having this conversation today, and I'm appreciative of it. Whether you agree with the approaches that I'm

getting us to think about or not, I think that's so important. So NRT is in a class of itself. I don't know whether that's a good thing. I don't -- I would suggest maybe it's not.

We risk getting to a point where we have more NRT choices. That's good. I'm from the Consumer Choice Center. So I want consumers to have more choices and more NRT choices is great. But I'm a little bit concerned, especially coming out of the last two days of TPSAC (ph), which was a very interesting conversations.

If we do better, if we're in this silo and we do better here on the NRT side, are we going to hear something along the signs of what we heard at TPSAC over the last couple of days, which is similar to this idea that well, NRT has gotten so good I'd like to see us get there, that what do we need these other products for because they have risks, they're not regulated the same way, part of the silo problem?

But what if we do better here? For those of you who didn't hear it in TPSAC, there was this fascinating line of questioning that maybe, from people

who are generally I don't think warm towards the idea of tobacco harm reduction, they're skeptics on the recreational side if you will, and the question is well ICOS, you know.

Over the next ten years maybe they'll be more uptake on e-cigarettes, which are presumably lower risk and then we don't need ICOS, which may be a little bit further along on that risk continuum, should why should we approve -- why should we recommend approving ICOS because e-cigarettes are going to become better or more well-adopted?

That type of thinking. Well, what if we apply that here to NRT? NRT's become better, so we don't want these other recreational products. I think that's a dangerous way of thinking, and I think we should be cautious of that and be aware of some of those unintended consequences. So I don't think NRTs should be in a class by itself.

Should FDA ask Congress for a more unified approach, where all products are regulated under the same division with the same public health goal in mind of reducing the harm from combustible tobacco and

minimizing the harm where possible from other forms of nicotine? I'm not saying it's a safe product, but I do believe that we live in the real world, and we should make policies based on that. So thank you.

DR. SHERMAN: Thank you for your comments. Does the panel have clarifying questions?

MS. SIPES: I think most companies would probably say that they think about consumer attitudes and consumer desire for choice when they develop their product.

I'm wondering if you have any thoughts or observations about things going in the other direction? In other words, in this space when we talk about nicotine-containing products including e-cigarettes, do you have any thoughts on how much consumers' attitudes towards not just those products but different modes of using them?

You know, use for satisfaction, medicinal use, long-term use, short-term use, all those things. To what extent those are shaped by what kind of products are available and how they're marketed.

MR. STIER: I think it's a two-way street, and

I agree with you, that companies think about, how did you phrase it, consumer satisfaction.

MS. SIPES: I think I was just thinking about what they believe consumers want.

MR. STIER: What consumers want. I have a weird way of thinking of this topic. I think consumers drive the market, and certainly the market plays a role in the choices available. But I think consumers want what they want. I think they crave more choices. I think there are a lot of consumers who like nicotine, and we have failed those consumers by telling them they have to not use any nicotine in the future, and we haven't given them to choices to consume that nicotine in a less harmful way.

Obviously, I'm only talking about adults. But I would like to see a world where people on their own make choices to have a product that they find satisfying and, if you will, enjoyable. I just don't want them to hurt themselves. I want them to have the choices so that -- consumers I don't think want to hurt themselves.

But they do want to have pleasure and they

want to enjoy things and they have stress and they, for whatever -- we rarely talk about, and I know this -- I hope this doesn't get censored out, the benefits of nicotine, right? Why do people smoke? They seem to like nicotine. That plays an important part of it. But I don't think consumers want to hurt themselves and die. They know.

So I think we need to do a better job. Not only does industry and consumer groups, public health groups, but the regulators themselves should be asking what do consumers want, and try to find a way where we can give consumers choices, where they don't have to damage their health nearly as much as they're doing now.

DR. SHERMAN: Yeah.

DR. WINCHELL: You mentioned a concern about the cost of failed attempts. I wonder if you had -- did you have thoughts about minimum standards for effectiveness for an absolute quit rate that a product ought to have in order to be considered effective?

MR. STIER: That's a great question. It goes back to this issue of different consumers, different

consumers are addicted to smoking at different levels. I learned something interesting in some other work that I'm doing, and it's like a social work concept. It's to meet people where they are, and different smokers are in different places, and I think it's our obligation in public health is to meet people where they are.

You take an older inveterate smoker as I've done, and you offer them Snus, I don't want that. It's not going to work. Have you tried the gum or the patch? (Chuckling), right. I'm not laughing. That was me imitating someone laughing. It's like that's not going to help me, and so -- and that's not to say the patch and the gum aren't good. They are good and they help a lot of people.

But they help certain people, and there are different tranches of people. I think this is what the FDA's talking about when it talks about the continuum of risk, right. Why is there a continuum of risk? There's a continuum of risk because well why would we accept higher risk products? It's because we need to meet people where they are and help them. The patch

works for some people and not others.

So I think we need to have a range of different products for a range of different people. There is no one thing that's right, and there should be lowest, the lowest possible risk products out there. There should be lots of choices, because people are different.

DR. SHERMAN: You have about 30 seconds left for a brief question and a very brief answer.

DR. DRESLER: I want to go back and address something you had brought up earlier. So I think reduce to quit is an important approach, and so many people don't quit abruptly and they go through the process, even a two week slip or relapse or whatever until they go on to a successful quit, or whether that's out to six months. So I think reduce to quit is an important way to move forward.

But I think it is important, and as you said people will be listening to this. Actually, the duration of smoking is critically important. So when you are reducing, you do need to reduce to zero because the duration of use is important for both your

cardiovascular risk, your cancer risk and your COPD risk, which are the important --

DR. SHERMAN: I'm sorry, I'm going to have to cut you off.

MR. STIER: I'll keep my answer very, very short.

DR. SHERMAN: You could submit to the docket if you don't mind. Thanks.

MR. STIER: I'll put it on Twitter.

DR. SHERMAN: Great, and just a reminder that everything said here is part of the public record. No one censors anything, and it's your opportunity to talk to us. We're not talking. So thanks to everyone. We're running ahead of time. So we can go to the next speaker. The last speaker before lunch will be Erika Sward, if she's present. Great, thank you.

Erika Sward

MS. SWARD: Good morning. Thank you very much for the opportunity to be here, and we really strongly support the Committee's work on examining these very important topics. My name is Erika Sward, and I'm the Assistant Vice President of National Advocacy for the

American Lung Association. I'm speaking today on behalf of the organization, which represents the 33 million Americans living with lung disease, many of which are caused by tobacco use.

The Lung Association also has been helping smokers quit over our decades of work. Over the course of just one year, the Lung Association convenes about 1,000 of our in-person face to face quit smoking clinics, and we help tens of thousands of smokers quit through our group counseling sessions, our online programs and our lung help line.

As this panel knows, approximately 70 percent of smokers say they want to quit, but this is an incredibly powerful addiction. The Lung Association urges the Nicotine Steering Committee and HHS as a whole to prioritize the 70 percent, the almost 26 million American smokers who want to quit. The Lung Association does not accept the idea that a certain percentage of smokers can't quit. One of our core beliefs is that every smoker can quit using all tobacco products.

The Lung Association also believes that a

significant portion of the remaining 30 percent of smokers who say they don't want to quit would still like to do so, but they're feeling defeated and believe that they'll fail at quitting. Of course, there's a good likelihood they will fail along the way before ultimately being successful.

It takes an average of eight or more quit attempts to most smokers to end their addiction for good, which is why the FDA's new Every Try Counts campaign is so powerful and important. But the FDA cannot look to or prioritize products or treatments that have not been found to be safe and effective in helping smokers quit, and switching to another tobacco product is not quitting.

In the fall of 2015, the U.S. Preventive Services Task Force, USPSTF updated the cessation interventions recommended, clarifying that all three types of counseling and all seven FDA approved medications are included. The Treating Tobacco Use and Dependence 2008 update and the 2015 USPSTF Update confirmed what works to help smokers quit, which the American Lung Association refers to as a comprehensive

cessation benefit.

Because the USPSTF designation of a A, virtually all private health insurance plans and Medicaid expansion plans beginning after October 1 of 2016 must comply with this updated rating. Although this must be enforced by HHS, if smokers are actually have real access to cessation treatments.

A bit of irrelevant tangent. The Lung Association found in a study we conducted in 2015 that of the over 500 plans that were in the state market places, only 17 percent of them were compliant with the USPSTF guidelines, underscoring that it's not enough for there to be treatments available from FDA, but smokers must have access to them as well.

We often hear "I tried the gum but it didn't work." Well, we know it's not just a one-size-fits-all situation, and that different treatments and combinations of treatments work for different people. The Lung Association believes that in many cases smokers aren't using the medications correctly.

Here are the three most common mistakes we see. Number one, smokers are simply not using the NRT

correctly. For example, with the gum, smokers are supposed to chew it until there's a tingling, and then park it between their cheek and gum until the tingling fades, and then chew it again until it tingles, etcetera, etcetera.

That's how the nicotine is absorbed, as we've heard earlier today. But if you chew nicotine gum like a regular piece of gum, the user doesn't receive the intended dose of nicotine. We also are concerned that many smokers take off a 24-hour patch well before the end of the 24 hours, and not use it according to instructions.

Number two, smokers are not using enough of their NRT, of a specific NRT, to save money or perhaps they don't like taking any medication. Many people effectively skimp on the amount of NRT they are using. Rather than chewing at least nine pieces of nicotine gum per day as recommended, they chew only four or five pieces. Perhaps unknowingly a highly addicted person uses the 2 milligram gum when they should be using the 4 milligram gum.

Number three, they aren't using the NRT long

enough. Instead of using it for 10 to 12 weeks, they're using the product for far less time. We often hear of people using NRT for the two to four weeks because that's what they receive when they call 1-800-QUIT NOW, or that's all their insurance plan will cover.

In April 3rd, 2017 MMWR article, "Quit Smoking Methods Used by Adult Smokers," researchers quantified the ten most common quit methods used by adult smokers. Not the ten most effective, but the ten most common. The study found that three-quarters of adult smokers used multiple quit attempts during their most recent quit attempt.

The most common was giving up all cigarettes at once. The second was reducing the number of cigarettes smoked, and the third was to turn to e-cigarettes, another tobacco product. Only when you get to the fourth most common method do you see smokers actually using evidence-based treatments. Only one-quarter, 25.4 percent, turned to the FDA-approved patch or gum.

So why is that? Why are a fourth of almost

the 26 million Americans who want to quit using treatments that FDA has found safe and effective while a third are turning to a tobacco product with its own toxins and carcinogens? We lay a lot of blame on the uneven playing field. Most smokers are desperate to quit and they're willing to try anything.

From the very early days, the e-cigarette industry has been willing to sell these desperate smokers the moon, with almost no response from CDER. If an e-cigarette manufacturer really believes its products can help smokers quit and end their addiction for good, they have and are free still to go through the rigorous clinical trials that the seven approved NRT products have.

But they must be required to demonstrate both safety and efficacy. FDA must hold these companies accountable and use the same standard of evidence for e-cigarettes as it did for the patch, the gum, the lozenge and the other quit smoking products. It cannot and should not allow a class of tobacco products to skate around the law.

No wonder smokers are so confused and turn to

products that have been almost free to claim anything they want, when the makers of these proven treatments are carefully limited in what they are allowed to say. CDER must use its existing authority to crack down on the unproven therapeutic claims that e-cigarette manufacturers made in the beginning and are still making today.

Here's one of the very first claims the Lung Association saw when the e-cigarette market first began to gain prominence in 2010. This is a poorly babblefish translated press release. This was many of -- one of many from a fictional press agent named Harry Heidi. It reads "The doctors recommend for traditional smokers the electronic cigarette or the e-cig product." It's rather reminiscent of the old "four out of five doctors prefer Camel" campaign that ran in the 40's and the 50's.

This press release then goes on to say, "Most especially for pregnant smokers, the doctor recommended it for them." Anywhere electronic cigarettes came out with this flagrant therapeutic claim in 2013. While most manufacturers are not this flagrant anymore,

unproven therapeutic claims still abound. In July of 2016, Klein et al. published a study "Online E-Cigarette Marketing Claims, A Systematic Content and Legal Analysis."

It concluded "In this marketplace, where the majority of smokers are interested in quitting, it is essential for the FDA to ensure that consumers are not misled into choosing products based on misleading or inaccurate health-related claims. In this way, enforcement by the FDA can lead to the promotion of public health and the protection of vulnerable consumers."

We can understand there was some confusion during the days of Harry Heidi, before the Satera (ph) case was settled. But since that time in 2010, the Lung Association believes there's no excuse for the inaction on cracking down on these unproven therapeutic claims.

In addition to cracking down on the unproven claims from both the e-cigarette manufacturers and retailers, FDA can also take another number of additional steps. Number one, one prevalent myth the

Lung Association often hears and still must counsel smokers against believing is the notion that if a smoker is wearing a nicotine patch, slips up and smokes a cigarette, they're likely to suffer a heart attack that day.

Not only could they have a heart attack, this myth is pernicious enough that many folks believe they will have a heart attack, but they often do not realize that the level of nicotine provided through NRT is significantly less than the amount of nicotine in a cigarette.

While the OTC NRT warning labels were changed in 2013, much of the language is still ambiguous. In addition, smokers may still remember the original warning label language that read "Do not use if you continue to smoke." Smokefree.gov has a page on busting NRT myths, but HHS must be proactive with its public education, much moreso than a web page if it is to end these falsehoods that have become so ingrained.

As I mentioned previously, the Lung Association believes that smokers are often not using NRT correctly. This starts to address the second

question posed by FDA for today's discussion. FDA can help smokers using the current OTC treatments more effectively, by working to develop clear and consistent labels and public education messaging for both prescribers and patients.

The low SES population makes up a large proportion of smokers in the U.S. today. The challenges this group faces include that they are less likely to have a regular health care provider, less likely to have the time and relationship with a real health care provider to have a meaningful conversation about using NRT, and they may not be able to get the information they need to fully succeed with these evidence-based treatments.

This should be one of the first populations that FDA considers when working with manufacturers in developing the labeling and any warning labels of NRT.

Number three, how can labeling be made more accessible and put into plain language? Why are the current directions less understandable and straightforward than the warnings? Do smokers realize that NRT has been found to be safe and effective, and

that any side effects are wholly less dangerous than smoking? FDA can and must take steps to address this.

Number four. There are a myriad of opportunities for additional FDA research, specifically in populations that continue to smoke at disproportionate rates. What interventions work better for the behavioral health population without reducing efficacy of common psychiatric drugs or causing more severe side effects?

There is evidence that the behavioral health population needs NRT longer, but much more research is needed into this population. Instead of making a behavioral health diagnosis and exclusion for criteria for city participation, it should be the focus of many more research studies in this area. OTC NRT products can and should be studied for use in combination. Would smokers benefit by using a patch for a steady state of nicotine and then the nasal spray to help overcome a craving?

While that may be practice for some cessation providers already, we still need the published evidence to back up the promising anecdotal stories. And what

FDA do to study the use of NRT in youth? We all know tobacco is a pediatric disease, and that the earlier someone quits, the better their health outcomes are. We need more focus of helping smokers quit before they even turn 18.

Here is heat map that shows adult smoking rates by state. It highlights that first, helping smokers quit cannot be FDA's job alone. Second, this map corresponds to the grades that these states earned in dark red in the Lung Association State of Tobacco Control report, which was released on Wednesday.

States that have a high tax, a smoke free law, invest in youth prevention and have comprehensive quit smoking coverage especially for Medicaid have lower smoking rates generally. And here is that map with cigarette taxes by state. The same states in red in the last slide are virtually the same states in red here, those with that low cigarette tax.

Our nation and these states will be dealing with tobacco-caused disease and death for decades longer unless a more robust intervention occurs. FDA and HHS as a whole certainly have an important role to

play in the prevention of youth use, and helping smokers end their addiction to tobacco products.

But these smokers also need evidence-based treatment with proven quit smoking treatments, not an unregulated tobacco product that continues their addiction. The Lung Association believes that HHS has a vital role to play in encouraging the states to muster the political will necessary to overcome the money and influence the tobacco industry still wields.

HHS and FDA can work together to incentivize states to implement evidence-based practices, especially around prevention and cessation. CMS especially Medicaid is at the heart of the cessation aspect, and it should be aimed at increasing access to a comprehensive quit smoking benefit. The Lung Association looks forward to submitting written comments to the docket, and thank you very much for the opportunity to present today, and I'd be happy to answer any questions.

DR. SHERMAN: Thank you for your comments.
Any clarifying questions from the panel?

(No response.)

DR. SHERMAN: Well, we'll look forward to receiving --

MS. SWARD: Last one before lunch. Thank you very much.

DR. SHERMAN: Right. Thanks very much. Thank you all. We will resume promptly at 1:05.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

1:05 p.m.

DR. SHERMAN: Okay. It's 1:05, so we'll reconvene. I hope everyone had a good lunch, and our first speaker this afternoon will be Dr. Mark Witt (sic).

Dr. Mark Watt

DR. WATT: So good afternoon. My name is Mark Watt. I thought it was the name which wouldn't be pronounced incorrectly but --

(Laughter.)

DR. WATT: So apart from having a name which evidently can't be pronounced, I lead the Medical Affairs Function in Europe and the Global Medical Function in nicotine development globally at Johnson and Johnson Consumer. I'm grateful to the FDA for the opportunity to address the public hearing and I'm heartened that you're undertaking a comprehensive effort to evaluate the regulatory approach and facilitate development of inhibitive or NRT therapies.

I believe a pragmatic approach to licensing and use will help more smokers enjoy the benefits of

newer, better NRTs, using more flexible ways and that will help to minimize the still considerable morbidity and mortality from smoking. So forgive me. We've chosen to reflect on international experience of NRT to address predominantly the first two questions posed in the briefing for this hearing.

That's fine, okay. So in Question 1, you ask might there be ways to improve upon the currently available delivery systems to yield new OTC NRT products that might be more effective, and what evidence would be needed to support approval of these improvements?

So these are -- these are vexing questions for regulators around the world, and especially so given the magnitude of the public health need and the need for flexibility in the approach to encourage new treatments to be made available. So we believe a global dialogue would be beneficial, so that novel approaches to regulation can be shared.

As I'll discuss in my presentation, some regulators have adopted appropriately flexible approaches that have enabled smokers early access to

novel NRTs. I think it's worth recognizing that nicotine is essentially now a generic active ingredient and existing formats of NRT differ only in the route of application or absorption, and the speed and extent of nicotine delivery. Generally, improvements in these parameters are sought in the interest of craving relief.

This graph on this slide shows the single dose pharmacokinetics of a number of our products, with Tmax the longest for the inhaler, as it's known here, and shortest for the oral mucosal spray, QuickMist. In terms of next steps, inhaled nicotine is the obvious place for NRT to seek further improvements in pharmacokinetics, and such technologies will, we believe, help smokers get the most from their treatment.

It's worth mentioning that choice of format is highly desirable. We don't see significant erosion in use of other formats when new formats are introduced. We seek increases in overall uptake. So this chart here shows the estimated global patient exposure data back to 2006 from Finnish product sales, and it shows

the proportion of exposure from different formats.

It's worth mentioning that since the introduction of the oral mucosal spray, which is the red part of the bars, there's been far greater growth in exposure from it than there has been any reduction from the use of gum. So generally, more choice appears to result in more use.

When considering new forms of flexible NRT, it's important to recognize that nicotine intake is self-titrated by the patient, and rarely significantly exceeds baseline nicotine intake from smoking. Systemic nicotine has an established and acknowledged favorable safety profile, although for some new formats obviously local tolerability studies would be advisable.

The reality is that the regulated nature of NRT has to date meant that it's not been able to move to inhaled formats, and at the same time it's significantly less regulated. No medicinal electronic nicotine delivery systems have been through at least three generations of development, with much controversy but obviously tremendous impact.

We believe that a step towards addressing this slight paradox would be to allow licensing of new NRT formats through bridging to the significant body of existing clinical data on NRT, by characterizing pharmacokinetic parameters within the range of existing NRT products.

So to summarize this simply, and you've heard a little bit about bracketing earlier on today, a new NRT format delivering plasma nicotine levels above a known level delivering efficacy and below a known upper reference tolerability or safety level could be assumed to function as for those reference formats, as it is bracketed within them.

Acceptance of this approach would reduce the need for placebo-controlled Phase III studies, and could be an accepted part of a fast track regulation pathway, getting new formats to smokers faster. This is not theoretical. The approach has been used in developed markets for more than a decade now, and this has facilitated early registration of new products without the need to repeatedly demonstrate that effective administration of nicotine offers benefits in

quitting.

So this is a chart, an illustration of the bracketing argument, and you've heard about it a couple of times. We're going to add a little bit more to this in terms of the upper limit, but as an example there's good evidence to support the efficacy of 2 milligram gum as a low strength NRT product, and also very good evidence to support the favorable risk benefit profile of high strength products such as the 4 milligram or even in some markets the 6 milligram gum.

Therefore, we believe it's appropriate to infer safety and efficacy of NRT products with these pharmacokinetic parameters fall within these two strengths, and that's the bracketing area that's on the chart, even if they are not strictly bioequivalent. The higher peak concentrations obtained from smoking are also pertinent when considering the NRTs. We'd ask the FDA to consider consulting with the MHRA in the UK to understand their approach to evaluating the safety of NRT, including with smoking as a comparator.

So the impact of such approach is exemplified by the experience we've had with QuickMist. A PK-based

approach to demonstration of safety and effectiveness as we've just described resulted in expedited licensing and availability to smokers two years before availability in countries where a Phase III trial was required.

Taken conservatively, 184-1/2 million cigarettes were -- of QuickMist were sold in the last two years in the UK alone. As I mentioned earlier, this impact was incremental to existing NRT, with very little in the way of reduction in the sales of other formats.

So the second question relates to how NRT can be deployed, and again I'll reflect on our global experience here, and how the best NRT usage in international markets helps smokers avoid returning to smoking. Now recognizing that tobacco dependence is a chronic disorder, an acute brief intervention may not suffice.

The process of quitting may be protracted or facilitated by more flexible dosing or the phase elimination of smoked tobacco. Offering such additional options to smokers will give them additional

approaches that they can take advantage of if they will help them. I'd like to discuss, I'd like to discuss these three.

So a combination of nicotine replacement therapy formats will usually employ a nicotine patch together with a flexible format such as nicotine gum, and the rationale for such combination treatment is threefold. So firstly, it optimizes the extent of nicotine substitution compared with levels from smoking, which has been found to improve cessation rates in its own right.

Secondly, combination therapy provides background levels of nicotine through a nicotine patch to manage withdrawal symptoms, while also enabling usage of fast tracking NRT to treat breakthrough craves. Finally, it enables both discrete application of a slow release nicotine format, while also addressing some of the behavioral aspects of smoking through the use of flexible formats.

So a number of studies have compared the efficacy of combination therapy with single NRT, and systematic reviews confirm the superior cessation rates

for combination therapy, with an increase in the odd ratio around 30 percent. Combination therapy is very well tolerated with a safety profile comparable to single, single format NRT. Evidence suggests that even with combination therapy, smokers are very unlikely to experience nicotine overdose.

Combination therapy has been practiced in the United Kingdom for more than ten years now, as a mainstay of treatment within national health smoking cessation clinics. Its use in the UK is widely recommended and endorsed by regulators, non-governmental organizations and a few opinion leaders.

So existing public health guidance in the UK recommends combination therapy, particularly for highly dependent smokers or those who have relapsed after treatment with single NRT.

So again, we've talked about reduction a couple of times today as well, and we believe it's important to understand that reduction is not an end goal in itself as far as we approach it, but is a step towards cessation. A recent study of UK smokers found that although two-thirds of them would like to quit,

only 12 percent are planning to quit.

This mismatch means there's an important opportunity to reach smokers who may consider reduction in smoking as a first step on their journey towards becoming a non-smoker. For these smokers, offering NRTs to facilitate reduction offers a step by step strategy which actually improves motivation to quit.

Evidence suggests that reduction with NRT as a first step towards cessation facilitates reduction and also improves cessation rates when compared with smokers who do not use NRT as they reduce. Concerns that smokers who also use NRT will overdose on nicotine are not founded, given that the data again shows that very clearly smokers can self-titrate their intake of nicotine to baseline levels while still undertaking reduction.

So there has been studies of this as well performed, and this chart plots the difference in cessation rates between NRT and placebo, the effect size of the treatment itself for three different populations. Brief advice is an established, accepted effective intervention for smoking cessation, and it

gives roughly a two percent increase in cessation rates when compared with placebo.

In studies of smokers who are not motivated to quit, the yellow bar, the effect was doubled for this two percent increase, and broadly similar to abrupt cessation studies of NRT in smokers who are motivated to quit. This is a useful demonstration that we can engage smokers with NRT, and facilitate cessation in smokers who are not motivated to quit through the medium of smoking reduction.

Another way of engaging more smokers is by offering more choice on the duration of NRT therapy. It's important to emphasize that here, that NRT should only be offered as long as there is a continued benefit. We know that tobacco dependence is a chronic condition. You've heard this several times. So it follows that treatment should not necessarily be given in the one short hit.

We know that many former smokers can still experience cravings months or even years after they have quit smoking. An NRT is many magnitudes safer than smoking, and extended use of treatments for

smoking cessation is extensively referenced in European and U.S. guidelines. So recent moves to liberalize this in the U.S., albeit some collaboration with a health care professional, are to be commended and built upon.

Extended use of NRT therefore offers smokers more flexibility by allowing them to progress at their own pace, and offers a lifeline to ex-smokers who may relapse to smoking. Yet current labeling in the United States restricts routine use without HCP interaction to three months. This is marked contrast to many other countries presented here, which allow longer durations of use from NRT from six months to 12 months.

Some countries such as the UK, I'm sorry for mentioning them again, allow open-ended use of NRT as a safer alternative with no maximum duration of use. But even prior to this, as far back as 2005, the UK Committee on Safety in Medicines allowed open-ended use beyond nine months if continued benefit was present.

So we'd urge the FDA to follow these many agencies by recognizing the benefits of extended NRT use with a quit attempt.

So amongst the questions posed by the FDA, we believe that international experience speaks directly to the first two for sure. Given the 40 year record of safe use of NRTs to help smokers quit, and the wealth of pharmacokinetic information that has been generated at this time, we believe pragmatic assessment of new products should recognize this, and use this as a means to get new products to smokers faster.

Secondly, making NRT more flexible in use will help more of those smokers avoid returning to smoking, by giving them the choice of not only products but approaches to help address their unique situation. So very strong evidence for these smokers that combination NRT therapy is proven to be more effective than single NRT.

We'd urge the FDA to consider this evidence, to allow smokers to receive the most effective interventions. Even in smokers who are not motivated to quit, smoking reduction can lead to quitting, and extended use of NRT offers more choices and flexibility for smokers, and accepted by many regulators worldwide.

Finally, it's worth stressing that these are

not abstract measures. They've been implemented in countries around the world for many years, and given our profound knowledge of nicotine and the significant experience of smokers in the real world, we believe that smokers here in the United States will benefit from new products made available sooner, and with the opportunity to use the treatments flexibly to avoid relapsing to smoking. I'd like to invite questions.

DR. SHERMAN: Thank you for your remarks.

Clarifying questions from the panel?

DR. WINCHELL: I do have a question. Could you say a little bit about the pharmacokinetic relative bioavailability studies? What is the mode of administration used in these studies?

Is it a metronome paced self-administration or a pre-specified interval of self-administration? Is it ad lib? How is, how are these situations handled if different circumstances yield different conclusions about whether or not the product lands in that bracket?

DR. WATT: So to date, these pharmacokinetic studies are based on potential maximum exposure. So they're dosed in line with that. So it's by a

metronome. It's also -- it's almost a stress test of the format. But if there's any situation in which you will see any potential issues with administration of maximum dose, you will see it during the course of the process of those PK studies. So you do get viable safety data from them as well.

DR. WINCHELL: And but suppose the other circumstances ad lib dosing would drop you below the lower limit of your bracket? Do they -- do you compare those?

DR. WATT: We wouldn't compare ad lib dosing that way, no. Again, this is a -- this is a demonstration of the potential of --

(Simultaneous speaking.)

DR. WINCHELL: Of safety. But you said it's also used to demonstrate efficacy?

DR. WATT: Absolutely. No, so there's a lower efficacy threshold and a --

DR. WINCHELL: A lower efficacy threshold when dosed in maximum use conditions?

DR. WATT: Correct.

DR. WINCHELL: Okay.

DR. SHERMAN: Other questions?

MS. CALLAHAN-LYON: You're talking about new products, correct? So in the -- how do they account for other parts of the product? So the chemistry, the excipients, stability, etcetera in this pharmaceutical bracketing approach?

DR. WATT: That's a fair question, and again that would be part of making the case for the equality of the product. So again, if you're going to introduce wildly new excipients, obviously you wouldn't be able to pursue this kind of approach. So again, within the boundaries of what is known to be safe and effective, I think you know in terms of excipients, that would be a consideration. We wouldn't propose putting vastly new things in.

DR. WINCHELL: Can I ask you? There's two questions and they relate to hey, you're saying it's important to have more choice. Your Slide 3, and I don't know if you can go backwards, there was no X or no Y axis.

So I couldn't tell if there's any difference between it looks like Year 2 and Quarter 3 '17, because

that looks, you know. So it's a little bit higher, but I don't know what that Y axis. So how do you take from this that more choice really is getting more people to try to quit?

DR. WATT: So I consciously removed that axis on the basis of there's potentially commercially sensitive information contained within it. So I can -- I can share in confidence the actual magnitude of that effect.

DR. WINCHELL: Maybe part of the docket then?

DR. WATT: This is -- this is extrapolated from sales data. So this is based on what is sold.

DR. WINCHELL: So you're telling me that there is a substantial difference between the start and the end?

DR. WATT: Absolutely, yes.

(Simultaneous speaking.)

DR. WINCHELL: A very large part of that is data up to the third quarter of last year. So we haven't got the final quarter of 2017 in there. So it's just for clarity, in case you thought I was sort of sharing, hiding a decrease in 2017 or something.

DR. WINCHELL: Okay, and then last one was on your Slide 13. You list all those different countries and showing that the U.S. is really, really restrictive. Do you have what those quit rates are in those other countries? I mean has it mattered that they're so much more flexible that, you know, a substantially higher proportion of people are actually quitting in those countries?

DR. WATT: I think that would be difficult to -- well, I mean you can plot smoking rates over time. So I guess you can look at the end effect in terms of proportion of people who remain smoking. That's even going to relate to being part of an anti-smoking effort.

I would have to -- we could probably find a proportion of that data. I can't -- I can't tell you off the top of my head what that looks like. But again, we could certainly look into that.

DR. SHERMAN: Can I just from when you used the word "efficacy" in response to one or two questions ago, you were still talking about basically pharmacokinetic bands, is that right?

DR. WATT: Correct.

DR. SHERMAN: Any other -- we probably have time for half a question? No, all right. Thank you for your comments.

DR. WATT: Thank you.

DR. SHERMAN: Our next speaker is Dr. Dorothy Hatsukami. How did I do?

Dr. Dorothy Hatsukami

DR. HATSUKAMI: That was a great pronunciation of my last name, so thank you, and I appreciate the opportunity to talk today and I think what you're going to see is some concordance or concurrence in results. So as indicated, my name is Dorothy Hatsukami, and I am professor of Psychiatry at the University of Minnesota, but I'm talking here on behalf of the American Association for Cancer Research.

This is an organization that has 37, over 37 thousand members and is the oldest and largest scientific organization in the world that's dedicated to the prevention and cure of cancer. Because smoking is responsible for about 30 percent of all cancer deaths, the AACR is firmly committed to find ways to

reduce cigarette use.

The comments that I am going to be presenting today are a result of discussions among the members of the AACR Tobacco and Cancer Subcommittee, which is comprised of leading tobacco control researchers. I would like to present this committee's subcommittee's comments on three topics. They include the need to improve nicotine replacement therapies, the need for additional indications for NRT and also the need for product labeling to educate consumers.

First, we believe that there is a need to improve on the current NRTs. Historically, the approval process for medicinal nicotine products has been very rigorous and regulations have been very restrictive.

In fact, efforts have been made to minimize the abuse liability and appeal of medicinal products to prevent the uptake among naïve tobacco users and also to prevent continued use or sustained use among consumers.

Unfortunately, these efforts have made -- have also minimized the uptake and possibly the efficacy of

these products among smokers who are trying to quit. Now the substitution for cigarettes is likely to occur if the alternative products provide higher, high levels of nicotine as well as faster speed of the nicotine delivery as well as provides the sensory aspects of smoking, and thereby increasing the appeal of the product.

Electronic cigarettes are electronic nicotine delivery systems which I will call ENDS, have the capability to do just that compared to the NRTs, and have been shown to lead to greater appeal, lead to greater substitution for cigarettes and more recently have exhibited great uptake for the purposes of smoking cessation.

A few clinical and epidemiological observational studies have suggested that ENDS can be an effective smoking cessation tool, especially if they're used -- if they are frequently used, yet there are major impediments for conducting the necessary smoking cessation trials with ENDS here in the U.S.

So therefore, our subcommittee recommends that the FDA actually consider a path of readily allowing

the independent investigators to test ENDS for smoking cessation, in order to facilitate the future development of these types of products as smoking cessation aids.

This committee also believes that evidence for safety and efficacy of the medication for smoking cessation continues to have -- continues to be of priority. Safety should be determined to be relative to continuous cigarette smoking, not just complete cessation, and randomized clinical trials should be conducted to determine the uptake and the efficacy of novel medications as compared to currently available nicotine replacement therapies.

Also, consumer perceptions of the marketing and product itself, among tobacco naïve individuals, should be conducted to determine ways to minimize the uptake among this population, and finally post-marketing surveillance must be in place. Now I'd like to talk about the subcommittee's comments on the additional indications for NRT.

We believe that there is sufficient evidence for efficacy and safety to support the use of

combination NRT medications, and we've heard this several times today. Studies have shown that combination medications are safe and more effective than monotherapies, as illustrated in the figure to the right where among those individuals assigned to monotherapies and even bipolar -- not bipolar -- bupropion plus lozenge, where among these individuals the combination of the nicotine patch and lozenge had the greatest sustained abstinence compared to placebo.

The recommendation for use of short-acting and long-acting NRT medications has been recommended by several reports including the Cochrane report, the U.S. Department of Health and Human Services Clinical Practice Guidelines for Tobacco Use and Dependence, as well as the National Comprehensive Cancer Network.

There are other indications that the FDA might consider. This includes prolonged use of NRT for harm reduction. That is, the use of NRT to completely substitute for cigarettes in order to reduce harm to health. So why would we advocate for this approach? Well, some smokers might find it very difficult to quit using nicotine-containing products altogether.

The Swedish experience with Snus, that is a low tobacco-specific and I just mean smokeless tobacco product, supports the use of non-combusted products to reduce mortality and morbidity as illustrated in the tables below. The first table on the left shows that Swedish Snus men, compared to the men in other European countries, have substantially lower death rates attributed to tobacco. This low rate has been associated with the low rate of smoking in this population, as a result of greater uptake of Snus among the men.

Now nicotine replacement products are substantially less toxic than Snus. Therefore, it stands to reason that using nicotine to reduce harm is a very reasonable approach. Now it's important to note that the AACR is not recommending cigarette reduction as a harm reduction approach, but rather a complete substitution of cigarettes with NRT.

The subcommittee also believes that long-term use of NRT -- believes in long-term use of NRT for cessation. We believe we need to frame nicotine addiction in -- as a medical condition that may warrant

more long-term treatment.

For example, in treating a psychiatric disorder you wouldn't say that you need to treat this psychiatric disorder for only two months. There are individuals that need longer periods of treatment. So extended duration of NRT might increase quit rates and recovery from smoking relapse in some smokers.

Another indication for consideration is pre-quit NRT use. So that is NRT could be used to reduce smoking initially, but with the ultimate goal of quitting. The reason for this reduce to quit indication is because not all smokers are ready to quit smoking. A study showed that almost half of smokers planning to quit for the next 12 months were interested in the gradual reduction approach.

Reducing to quit with NRT is more effective than placebo, as illustrated in the -- oops, sorry about that. Forgot to advance the slide. So as illustrated in the figure there in this particular PowerPoint, this was a study that conducted by Shiffman, and it showed that those individuals that were assigned to the active NRT, which is in the gray

bar as compared to the open bars, the white bars, which is placebo, did much better in terms of cessation across time.

Now finally reducing to quit results in comparable quit rates as abrupt cessation, indicating that reduce to quit does not compromise quitting success. I'm going to skip over this slide. Now we believe a reduced risk claim should be added to the product label. For example, this label can state nicotine replacement therapy is substantially less harmful to health than cigarette smoking. Now why would we want to do this?

Well unfortunately there are a significant number of significant misperceptions or lack of knowledge on the harm of nicotine and NRT amongst smokers, as well as health professionals. So misperception has been associated with reduced uptake and less optimal use of NRT. Therefore, the reduced optimal NRT use results in less efficacy.

So in summary, the AACR subcommittee recommends to the FDA the following: One is facilitate the improvement and appeal in nicotine delivery to NRT

to increase its uptake and efficacy; approve NRT for combination therapies. We believe that the evidence is there and the safety evidence is there.

Consider approval of NRT for harm reduction, extended use, reduce to quit; and also add a reduced risk claim on package that clarifies the misperceptions of relative harm and harm of NRT. Thank you.

DR. SHERMAN: Thank you for your comments. Are there clarifying questions from the Committee?

DR. WINCHELL: I do have a question. Can you help me understand the distinction between the scenarios described in Slides 9 and 10. You've used the term "harm reduction" but it doesn't sound as if the outcome measure is a direct measure of harm, but instead documentation of continued refraining from cigarettes. So this would be more like a maintenance of abstinence type of scenario. How is that different from long-term use for cessation?

DR. HATSUKAMI: So in terms of the long-term use, it's really to the goal would be abstinence, complete abstinence from --

DR. WINCHELL: But isn't that also what you

said about the long-term use of NRT to completely substitute for cigarettes. That's also abstinence, right? Or you mean abstinence also from nicotine?

DR. HATSUKAMI: Yes.

DR. WINCHELL: Oh, I see okay. A longer term course of treatment ultimately ending with taper? Got it.

DR. HATSUKAMI: Yes. That's what -- that was what I had intended to say.

DR. WINCHELL: Thank you, thank you.

DR. SHERMAN: Other clarifying questions?
Thank you for your remarks.

DR. HATSUKAMI: Okay, thank you.

DR. SHERMAN: Our next speaker is Dr. Saul Shiffman.

(Off mic comments.)

Dr. Saul Shiffman

DR. SHIFFMAN: You've already seen my slide, so never mind. Thank you to FDA, both CTP and CDER for convening this Committee, but more importantly, as others have said, for initiating what we all hope will be an ongoing process to improve how we help smokers.

I'm not going to address particular regimens or indications, in part because I --

Well, not only have you heard a lot about that already, but in part because I think the gateway to those changes really require more of a reframing about how the Agency looks at nicotine products, both medications and others. So I think the reframing is the most important thing.

I will say I am surprised and gratified by the degree of consensus in what we've heard today. I'm also distressed because just about everything I'm going to say has already been said, but I will say it anyway. To introduce myself, I'm a professor at the University of Pittsburgh and also a consultant with Penny Associates.

The material I'll be presenting represents my own views, but I want to both do a disclosure and say a little bit more about my professional history because I think it may help understand sort of where I'm coming from.

So I've been doing research on smoking and cessation for about 45 years, which is to say I started

as a child. I've had NIH funding for work for almost all of that time. But I've also worked with pharmaceutical industry and interacted with CDER on that basis. I consulted with GlaxoSmithKline for 20 years on smoking cessation.

I'm proud to say I had a role in helping switch nicotine replacement products to OTC some 20 or so years ago, and that did result in a substantial increase in utilization. With colleagues, I hold two patents on a faster-acting nicotine gum, but I'm not going to talk about that product, but have more recently been consulting first to NJOY from whom you heard this morning, and to Reynolds, from whom you also heard on harm reduction products. Not cigarettes but harm reduction product.

I am not speaking for Reynolds or BAT. Indeed, I haven't shared this presentation with them. So what you're going to hear is my views not theirs. I'm really going to make two points. One is the ways in which nicotine is different from the drugs CDER typically considers, and then secondly what the relative roles are of CDER and CTP type of products in

this public health enterprise.

So nicotine is really pretty different from new drugs that CDER would normally consider, because you seldom consider a drug where the user is already taking the drug, in fact taking it at higher doses and unfortunately in a highly toxic vehicle, that is cigarette smoke. That should certainly inform the concerns that one would have about safety. You're not introducing a new drug.

At least in the OTC world, I try to think about another drug that has a role in preventing death and really couldn't think of one. So as you've already heard, half of all continuing smokers will die as a result. I mean in some ways, the framing ought to be like an oncology drug or maybe an HIV-AIDS drugs, where you have to consider what the alternative is if you don't treat the condition.

I think part of the issue for all of us and for the Agency, as it is for smokers, is the way in which we discount long-term risk, and I mean discount in the behavior economics sense, which is we don't react with the same urgency to things that are distant.

So 64,000 deaths per year due to opiate overdoses is a national emergency, and indeed it is.

But then what is 480,000 deaths per year due to tobacco? Surely that should invite a great sense of urgency. And for that reason, I think as others have said, that smoking and not simply breathing pure mountain air should be the comparator for safety of NRT and nicotine products.

Nicotine is also different because we have so much knowledge about efficacy. There are over 150 randomized clinical trials in the Cochrane registry which by the way is only a subset of the literature, because they have very high standards. Nicotine's been shown to be effective administered every which way. I think there might be a couple of orifices we've left out.

So there really isn't a need to reinvent the wheel in that sense, and as you've heard I think in more detail than I need to go into, the regulators in other jurisdictions, particularly in the UK, have recognized this and allow what's been referred to here as pharmacokinetic bracketing to be a primary basis for

approving products, and that is a very progressive and reasonable approach.

It's not only efficacy that's been repeatedly demonstrated, but safety. So in the U.S. alone, NRT products have been on the market for well over 30 years, and OTC as OTC products for well over 20, without significant problems. So in a sense the fundamental safety is very well established.

Nicotine is also different in another way. Most civilians, if you will, people walking around, are not familiar with new drugs being considered by CDER. In contrast, I think every person in America could tell you something about nicotine and probably thinks they know something about nicotine, and unfortunately most of what they know is wrong.

So there are huge misperceptions about nicotine. Smokers, non-smokers and even physicians believe, contrary to fact, that nicotine is the main cancer-causing agent in smoking, and indeed there's lots of survey data to show that people think, many people think that NRT is as dangerous as smoking. FDA is not actively trying to correct those misperceptions,

and I think FDA unintentionally and inadvertently may be perpetuating them, and let me show you what I mean.

This is the label for the OTC nicotine lozenge standard drug facts label. But I want you to look at it from the perspective not as people who know about drug facts, but as a naïve person on the street. So what you see is the label contains 629 words, including 223 words devoted to warnings. Does not convey safety.

It also has 306 words related to directions, which would give you the sense that this is a very difficult product to use. I want to contrast it to something else. This is the longest of the current warnings on a pack of cigarettes, which has 18 words, and by the way these are to scale.

So inadvertently, although that's obviously not the function or the intention of the label, what we communicate to smokers is that these are dangerous, difficult to use products.

So we should perhaps not be surprised if people are not eager to use them.

Finally, as others have pointed out, the world has changed. There are already millions of people

using nicotine products in the form of electronic nicotine delivery systems, many of them with implicit or explicit intention to use for quitting, and that should really change how we think about things.

Ideally, we want to provide people with appropriate alternatives for using those in a regulated way with directions, with proven clinical efficacy.

So lots of ways in which nicotine is different and should be, I would argue, considered differently by the Agency.

Having said that CDER has implied and I believe that CDER has a very important role in promoting innovation in nicotine products and NRT, the question is is CDER really the right home for all nicotine products? My answer is no, that rather there is a role, a very important public health role for nicotine products outside of CDER and outside of treatment for smoking cessation, and I want to talk about why.

I think there's a very important history that's been alluded to and that we should learn from. So I have the scars and gray hairs, where I have hair,

from having tried for decades to encourage people who are quitting smoking to use NRT to help. Despite that, we've had really pretty modest success at getting people to use these products despite uniform encouragement from public health and medical authorities to encourage that.

But look at the history of ENDS, where people are -- I mean with NRT, sometimes you hardly can give it away for free. In contrast with ENDS, smokers have been lining up to pay their good money for these products, in this case despite discouragement and warnings from medical and public health authorities. So why is that?

And one reason that people have alluded to and rightly so is that the products are better. They deliver nicotine more aggressively; they have other aspects, sensory aspects, flavors. The very things that cause some concern when you bring a product to CDER are the very things that have made these products have enormous reach, much greater than that of NRT.

But I think it would be a mistake to think that it's just the product. There's a cultural fit

between ENDS and smokers that we need to recognize. So adopting a medication requires that you, again from the smoker's perspective, cave into that finger-wagging you're bad, you ought to quit. One of the things we know about smokers from lots of research is that they are very rebellious. So that's not exactly the approach that appeals to them.

But also, you have to frame yourself as having a medical addiction problem that requires medication. You have to commit to quit right now, abruptly, and to use a medication for a short time in a very strict regimen. That is not where everybody is. Rather, people want to explore -- a lot of smokers want to quit, but they have their own pace and way of getting there.

I thought it was -- this was a very good quote from the UK Center for Tobacco and Alcohol Studies, which pointed out essentially this point, that one of the great strengths of e-cigarettes is precisely that they're not medicalized, that they're posed and presented as consumer products and that means they have higher reach.

If we think about it from a public health perspective, the population impact is a product of both efficacy and reach. So that getting reach, presenting products that people will actually use is very important.

This is just an anecdote. These are all quotes from the *New York Times* about Jeannie Cox. I'll give you a couple of seconds to read that, and the key section is the part in the middle that I've italicized, which is it wasn't her intention to quit. That wasn't what she was trying to do, and yet having adopted the product with a different intention, she in fact ended up quitting. Now I realize that anecdote is not the singular data. There's actually a lot of data, and you've seen some of it already from the J&J presentation.

There's a lot of data that if you engage people systematically selected in these studies to not be ready to quit, and you give them NRT and suggest they might want to reduce, what you do is increase quitting. In fact, that's an improved indication in more countries than I knew of.

It relates to an important harm reduction principle, which is you meet people where they are. You don't say well, you're just going to keep smoking until you're ready for what I have to offer and then we'll talk, but rather you try to meet people where they are.

So in summary, I think for any of these particular changes in labeling to be considered, there needs to be a reframing, and with that reframing CDER and FDA could really encourage innovation in the NRT space, and at the same time we should recognize that smoking cessation medications through the CDER pathway are not going to be the only kinds of nicotine use that will help public health. So thanks for your attention and glad to take questions.

DR. SHERMAN: Thank you for your presentation. Clarifying questions from the Committee? I have one. On the implicit communication of risk slide you had with drug facts box --

DR. SHIFFMAN: Sure.

DR. SHERMAN: Has that been studied, that the number of words or the placement or the fact that

they're warnings is felt to be risk, present risk?

DR. SHIFFMAN: No, not that I know of. What there are data on is that there are huge misperceptions, and the people believe not only that nicotine is dangerous but specifically that NRT is dangerous and in some cases as dangerous as smoking.

DR. SHERMAN: Thank you. Our last scheduled speaker, registered speakers will Ben and Nussy Levilev.

Ben and Nussy Levilev

MR. BEN LEVILEV: I guess they saved the best for the last, right? I'm Ben and this is my brother Nussy. So yeah, we're here to propose safe and natural smoking cessation products that apply to all of the concepts to consider from the FDA *Federal Register*. The methods and solutions we are presenting to the FDA are not drugs or medication; however, they do indeed offer relapse prevention and craving reduction that help smokers quit smoking and overcome the urge to smoke.

The products can be used alone and in combination with OTC NRT products or medication. So to

get started, I have, you know, a majority of 70 percent -- roughly 70 percent of adult smokers in the United States report that they want to quit, and nearly half of them take a quit attempt each year.

Many of those quit attempts involve the use of NRT products, which are designed to help people quit smoking by supplying controlled amounts of nicotine to ease their withdrawal symptoms. So although OTC NRT supplies controlled amounts of nicotine, it's very likely to keep smokers addicted to nicotine and smoking, rather than actually help them quit.

To give you a scenario, would you give an alcoholic small amounts of alcohol to stop drinking alcohol? So why would you give a smoker more nicotine to quit nicotine? I'm not saying that it's not helpful, but just an example.

The issue of only using nicotine products and medications is that most OTC NRT products focus in replacing the nicotine addiction with more nicotine, and essentially keeps the smoker addicted to nicotine by either using gum or patches or e-cigarettes continually, but I'll get back to that.

In addition, some smokers are hesitant to use NRT and medications since they're concerned about the side effects that it can cause, and not only that, like what many have mentioned is that NRT, nicotine replacement treatments and medications, are not recommended for pregnant women and patients with health conditions, which leaves them with little or no option to use for quitting.

Finally, many smokers struggle to quit due to being heavily dependent on the behavioral patterns of smoking, which include oral fixation and the hand to mouth movements, and a survey shows this to be one of the main reasons for failure and a major cause of relapse when a smoker stops smoking, which is using nicotine replacement products.

Treating these symptoms and using safe nicotine-free remedies plays an important role in the long-term smoking cessation process and relapse prevention, and providing natural smoking cessation remedies offers all smokers a variety of safer alternatives and options that can help them stop smoking.

The goal of our product is to end the use of nicotine, and the first product we're presenting is Harmless Cigarette. It's a therapeutic patented habit replacement that's been developed to help smokers satisfy cravings that overcome the urge to smoke naturally. It focuses on satisfying both the psychological and physical hand to mouth addiction, which most smokers find difficult to overcome when quitting.

Harmless Cigarette is not an e-cigarette. Harmless Cigarette combines therapeutic effectiveness with harmony of scent and aroma. It's engineered to replicate the feel and draw, and to mimic the real -- to mimic a real cigarette using a proprietary air filter. You don't light it, you don't charge it. No smoke or vapor is inhaled directly, and it can be used any time, anywhere, including in all non-smoking areas.

This natural smoking cessation method helps smokers gradually defeat their nicotine and smoking addiction without any drugs, nicotine or side effects, and since Harmless Cigarette is not a medical device, it's simply a powerful therapeutic tool to help

increase a smoker's chance of quitting, Harmless Cigarette is best to use by itself.

However, it can be used together with NRT products and smoking cessation medication, since it doesn't interfere with any nicotine or prescribed smoking cessation medication. It can be very helpful and effective when used together either with the OTC NRT or medication. Harmless Cigarette helps smokers increase their chances of quitting, and the elements of the products are not only considered to be effective methods for smoking cessation; they also help promote feelings of relaxation and calmness while reducing a smoker's craving to smoke.

Let's see. Just another side note. Our products and methods open up a novel area of research in smoking cessation which can be tested and studied to prove their efficacy as safe, natural smoking cessation products and alternatives. Now therefore, it is a safe alternative. Harmless Cigarette is a safe alternative which can be used by all smokers that want to quit, including pregnant women, patients with COPD and others that have other health conditions.

A clinical trial has successfully been completed, which proved that this replacement therapy method provides a solid substitute for oral fixation and both the psychological and physical hand to mouth addiction. We also have several other safe nicotine-free natural smoking cessation aids which are currently being developed and tested. We can talk about that separately, and it comes in various delivery methods.

So just something from the *Federal Register*. It says the FDA has approved two types of prescription NRT products, a nicotine nasal spray, nicotine inhaler, and three types of over-the-counter OTC NRT products, a nicotine gum, transdermal nicotine patch and nicotine lozenges. Now most of these products have been approved for over 20 years.

The use of approved prescription and OTC NRT products is generally considered to be doubled -- generally considered to double the likelihood of successful quit attempts, although they're a variation of efficacy among the types of products. However, there are no natural solutions or safe solutions for products listed on the FDA's web page of smoking

cessation products for smokers to use to quit smoking.

We are confident that the FDA will see an extremely high successful rate of smokers that have been able to quit smoking using Harmless Cigarette in combination with either by itself or in combination with medical or OTC NRT. At the end of the day, the benefits of Harmless Cigarette outweigh any risk. So in conclusion, we're not here to seek any approval from the FDA as our product is not a drug or a medical device.

We're simply suggesting for the FDA to acknowledge that a natural smoking cessation method or alternative can help make OTC NRT or medications tremendously more effective when they are used together with Harmless Cigarette.

We believe that the results of FDA, either certifying or recognizing Harmless Cigarette as a safe smoking cessation alternative will ultimately help smokers overcome cravings and increase the chance of successfully quitting.

Together, we can save -- wait a minute.
Together, we can save lives and create a smoke-free

world, and yeah. Oh, one more thing. One second. I'm not finished. We'd like to thank the panel and all those who put this public hearing together to discuss this important matter, and I'll be happy to take questions.

MR. NUSSY LEVILEV: I want to add to follow up on something that Mr. Myer had said regarding driving down cigarette use, and the FDA has banned tobacco companies from advertising their product. But tobacco companies still have a free rein to have influencers and celebrities which have a huge following with youth to post photos, videos on all social media platforms of using their products and promoting it, including movies and television, and they should consider to have warnings when they show those products and the tobacco use in movies and television, and they should also be required to have skull and bones poison icon on their products.

DR. SHERMAN: Thank you for your comments. Any clarifying questions from the Committee?

DR. DRESLER: Just one quick question. You mentioned that you had a study. Did you have a

cessation rate?

MR. BEN LEVILEV: Yes.

DR. DRESLER: So and what was the size of the study and the cessation rate?

MR. BEN LEVILEV: It was a study that was conducted with 120 participants that were divided into two groups. Half of them received just a nicotine replacement product and the other half received the nicotine replacement product in combination with the Harmless Cigarette, and it was a 68 percent higher success rate in the group that quit using Harmless Cigarette in combination.

We're actually conducting another study with a -- with Harmless Cigarette in combination with varenicline (ph). So just to get some more data on using either an NRT product or a prescription medication.

DR. DRESLER: So you said 68 percent higher quit rate, but can you tell me what the quit rate was in each of those two arms?

MR. BEN LEVILEV: Yeah. I can actually provide it in the docket.

DR. DRESLER: In the docket? Perfect. Thank you so much.

MR. BEN LEVILEV: Yeah, no problem.

DR. SHERMAN: Any other clarifying questions? Thank you for your comments.

MR. BEN LEVILEV: No problem. Thank you.

MR. NUSSY LEVILEV: Thank you.

Open Public Hearing

DR. SHERMAN: That concludes our scheduled portion of this hearing. We'll now open the Open Public Hearing. Our first speaker is Maria Gorgova (ph), Senior Principal Scientist from Altria Client Services.

(Pause.)

DR. GORGOVA: Hello? Can you hear me? Okay. Good afternoon. My name is Dr. Maria Gorgova, and I'm senior principal scientist in Regulatory Affairs at Altria, the market leader in U.S. tobacco industry. While this public hearing is focused on FDA's approach to evaluating NRT's products in their role in harm reduction, it's also important to keep in mind the role that other alternative tobacco products can play.

At Altria, we believe a portfolio of FDA authorized alternative products that meet evolving customer preferences is critical to reducing the harm caused by smoking. Today's meeting is part of FDA's new comprehensive plan to regulate tobacco and nicotine. As part of the plan, FDA clearly acknowledged the continuum of risk and encouraged innovation in alternative tobacco products.

As FDA implements its plan, I encourage the Agency to consider the following three concepts that need to be addressed in order for FDA's plans to be successful. First, understanding about tobacco consumers and their preferences should be front and center. There are about 40 million smokers in the U.S. today.

According to CDC in 2015, 68 percent of them wanted to stop smoking, but only about 55 percent made a first year quit attempt. Of those, about 31 percent used cessation counseling and medication when trying to quit, and only about seven percent succeeded.

While these numbers show a demand for such intervention, they also highlight the need to develop

more effective cessation medications, which is the reasons for today's hearing. At the same time, there are millions of smokers who for various reasons are not interested in quitting. So what can be done for them? Based on our data, more than 20 millions of smokers in the U.S. are looking for innovative alternative tobacco products.

As manufacturers, we must continue to invest in the development of various products and the science needed to substantiate reduced risk claims. It is also critical that customer misperceptions about the health risk of the nicotine and the health risk of the tobacco products are corrected. Right now, customer do not have the information they need to make informed choices.

For example, a recent survey showed that 70 percent of smokers mistakenly believed that nicotine results in heart attack, stroke, lung cancer and oral cancer, and today compared to four years ago, twice as many adult smokers in the U.S. believe that electronic cigarettes are equally or even more harmful than conventional cigarettes.

FDA and other government agencies should play active role in correcting these misperceptions, and we encourage them to do so. Manufacturer, however, have a role to play as well by filing MRTP applications for values potentially reduced risk products. Finally, FDA's comprehensive plan for nicotine should encourage innovation and provide clearly defined viable pathways to bring some products to the market. This includes NRTs, as well as a variety of other non-combustible tobacco products. Thank you.

DR. SHERMAN: Thank you for your comments. Are there any clarifying questions from the panel?

(No response.)

DR. SHERMAN: Thank you. Our next speaker is Mark McQuillan, Managing Director from Nicobrand.

MR. McQUILLAN: I have no comments.

DR. SHERMAN: Pardon me? You what? Is he gone?

MR. McQUILLAN: Sorry. I have no comments to make.

DR. SHERMAN: Oh, thank you. The next speaker is Jed Rose, professor from Duke University.

DR. ROSE: Good afternoon. I'm a professor at a Duke University, but I'm expressing my own opinions here, and by way of background, I've been in the field of smoking cessation treatment research since about 1979, was involved in the original development of the nicotine skin patch in the early 1980's, Chantix in the 1990's and more recently novel nicotine inhalation systems.

But my comment here focuses on the difficulty that's being created by current FDA policy in essentially blocking progress toward evaluating the efficacy of e-cigarettes in smoking cessation treatment. CDER has taken the position that obtain an IND even for a short-term smoking cessation study, it is required to conduct animal inhalation toxicology studies.

These studies cost many hundreds of thousands of dollars, which no academic lab funded by an NIH grant can afford to do. I currently serve as principal investigator on a National Institute of Drug Abuse P-50 Center Grant, and two years ago under this grant was supposed to have launched a study to evaluate the

efficacy of e-cigarettes, either alone or in combination with nicotine patch for smoking cessation.

I think this is a very promising approach because of the literature, which we've already heard about today, showing that the combination, combination NRT treatments such as patch plus lozenge or patch plus gum is more effective than nicotine patch alone. The use of the patch decreases the burden placed on the e-cigarette to achieve adequate nicotine delivery.

The pharmacokinetic studies that we've also heard about have shown that for many types of e-cigarette at least, the initial users obtain sometimes only about half of the peak levels of nicotine as obtained from combustible cigarettes.

A typical mid-strength combustible cigarette delivers about 200 micrograms of nicotine in a standardized volume of puff, whereas the typical e-cigarette is more like 100 micrograms, about half of that. Now some users will learn to compensate, take longer puffs and eventually match nicotine deliveries from an e-cigarette. But initially, it could be a serious burden or problem for smokers to make the

successful transition.

So by combining a nicotine patch with an e-cigarette, the hope is that it will allow smokers to more easily achieve both their peak nicotine levels and maintain trough levels to achieve success. But because of the CDER policy, we and others in the field have been totally blocked from conducting such studies, and as I say we were supposed to start this study two years ago.

In that time, approximately a million more American smokers have died of smoking-related disease. By the way, people cite the 480,000 deaths per year figure, but if you look at the Carter et al. *New England Journal of Medicine* paper in 2015, they estimate more like 540,000 deaths a year.

In any case, I'm not blaming CDER for the epidemic of tobacco smoking, but I do think that the Agency could do more to help reverse the devastating status quo than has been done to date, and to be less obstructive in standing in the way of investigators who are trying to do studies to inform smokers.

So while we can't stop the carnage overnight,

it will be helpful to have the knowledge gained from such clinical trials to inform both smokers about what actions they can take to break free of addiction to combustible cigarettes, and also inform the Agency. For example, CTP, in evaluating the public health impact of MRTPs, needs to be able to factor into their population modeling how many people might use e-cigarettes alone or in combination with other NRTs to achieve smoking cessation.

And so what I urge, I urge both CTP and CDER to work more effectively together to help allow researchers such as myself to conduct these types of studies, to provide vital information on the therapeutic effects of e-cigarettes, without having the essentially impossibly high bar to meet of providing animal inhalation toxicology studies before launching such studies. Thank you.

DR. SHERMAN: Thank you. Any clarifying questions?

(No response.)

DR. SHERMAN: I have one. If you -- I gather you don't believe the animal toxicology is necessary to

assure the safety and welfare of the clinical trial participants. Is there any body of data you feel the FDA should require before allowing an IND to proceed?

DR. ROSE: So I think with marketed e-cigarette products, where there have already been, you know, published reports, the Cochrane report for example and others, you know, showing that people are not dropping dead from short-term acute use of e-cigarettes, that in a short-term clinical trial of let's say eight weeks' exposure, that there shouldn't be the need for animal inhalation toxicology at this point.

DR. SHERMAN: Thank you. Okay. Our last speaker is Scotty Freeman, who is self-employed at a company called Hippie and the Hound.

MR. FREEMAN: Hi guys. How's everybody doing? I'm going to -- I'm going to try not to cry. I get very emotional about vaping products. I'm, you know, and smoking and the whole nine yards. I get very emotional of it. Now I've listened to everybody here. Everybody's very educated, you know. You seem like very nice people. One thing that I don't think you

guys understand is us, the smokers, the people, okay.

We live a different life, all right, and quite frankly I think somebody said we don't care what you think about us. We don't, and they don't care about you. They just want to live their life and enjoy it, and they enjoy smoking and they enjoy nicotine. They know it's killing them. I knew it was killing me, but I didn't care. I kept doing it.

Now about four years ago, I opened up a vape shop. Did not want to quit smoking cigarettes, was not going to quit smoking cigarettes. But on December 8th, 2013, I lit up my after work cigarette and it tasted like death, and I have not had a cigarette since. I represent all of those people are just like me, all of my customers.

I have witnessed nothing short of miracles in my shop. People who are getting ready to have their foot amputated be able to save their foot. People who couldn't have surgery because they smoked be able to give up their cigarettes for the first time in 20, 30, 40, 50 years, and have surgery. Life-saving surgery, literally saving their lives, and we've reached out.

It's the flavors. It's the enjoyment.

We made not smoking fun. Imagine that, you know. I mean we all tried the patches. We all tried the gums. We all tried the pills, you know. We've tried these things, and lo and behold this comes along, and all the while we're hearing dodgy studies, people are scaring them. Oh, you might get the popcorn lung. Now come on guys. Let's tell these poor people the truth. Just a little bit of the truth. You know why we're studying it and we're trying to figure out.

You know, if you saw the ladies that came into my shop that had smoked for so long, and they come back in in two weeks after visiting my shop, and they're like oh my God, I haven't smoked a cigarette in two weeks! I can't explain why the flavors is so important. I really can't. Now I tried to close my shop up after you guys deemed it a tobacco product, and after my government taxed me at 40 percent and they demonized me. I was like I'm done with this, and my customers begged me not to close up because they've tried everybody else's e-juice and mine was the best.

I'm just like please go somewhere else. I

don't want to make money off of this. I don't want this as a business, and you know, I mean this has been the most -- I can't believe I'm here talking to you right now. This is not my life, right. My life is having fun. My life is making ice creams. My life is going to rock and roll concerts. It's not talking to public panels here telling you tell the people the truth.

It's not that hard. England told us two years ago that they're 95 percent less harmful. We're just talking about harm reduction here. It's not brain surgery, you know. Anybody can practice harm reduction. You know, I'm telling you I've had customers that were dual users for two years, and the minute they quit smoking, you know, -- their life comes back.

I have a number of them that have gotten off completely off of nicotine, off of vape. I've had many of them that have tried and just they need their nicotine, and they need the flavor that I produce, you know. It's like I've begged them to go to other places.

I encourage you guys to instead of talking amongst yourselves, go to a vape shop. Go sit and chat with some vapers. Go find some guys with the gray hair like me and chat with them, and see what this product has meant to them. You know, my shop was at one time probably the best peer to peer smoking cessation center in Erie, Pennsylvania, and I'm telling you there's a lot of smokers in Erie, Pennsylvania.

I welcome you guys to come to my shop. I've got an ice cream shop right next door and come check out, you know, what it's like down in not so pretty areas of town and talk with my customers. I hope you guys have a beautiful day. Much love to everybody and, you know, maybe work with us to help save some lives.

DR. SHERMAN: Thank you for your comments.

MR. FREEMAN: Anybody have any questions?

DR. SHERMAN: Well, any questions, clarifying questions from the panel?

(No response.)

Concluding Remarks

DR. SHERMAN: On behalf of the FDA panel, I would like to thank all presenters and anyone in the

audience, whether you attended in person or via webcast, for participating in today's public hearing. We greatly appreciate your attention and your interest and sharing today's presentations.

In addition, I would like to recognize the folks involved in putting together this hearing. Dr. Allison Hoffman, Theresa Wells, her colleagues at DRT, the Great Room staff, the panel, everyone in the Centers who in addition to the extra disruption and time commitment imposed upon all of us by the orderly shutdown and then standing back up, managed to make sure this very important hearing went off without a hitch, except perhaps for my inability to pronouncing these names. Other than that, it was quite an impressive feat.

As a reminder, and we've said this repeatedly but I can't over-emphasize it, we strongly encourage you to submit comments to the docket, and any data that -- any data or high-quality evidence you think would be important in informing our decision-making and our actions. The docket will be open until February 15th. If you'd like details on how to submit the comments,

Theresa, go and put the slide up with the -- for the website? Great, thanks.

If you'd like details on how to submit comments to the docket, and we have placed copies of the *Federal Register* notice at the registration table. For the folks on Web-X, the slide is here. A transcript from the hearing should be posted to the hearing website within 30 days. We will provide copies of today's presentations upon request. The contact information is available at the registration table, and for the folks at home it's on the slide.

On that note, I close this public hearing. Thank you, and have a safe trip home.

(Whereupon, at 2:21 p.m., the public hearing was concluded.)

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I, Natalia Thomas, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



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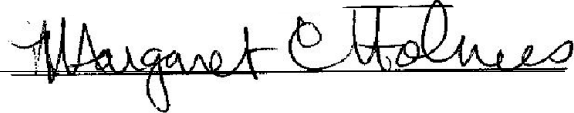
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February 8, 2018



Margaret Caraway Holmes