FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

(TPSAC)

Thursday, January 19, 2012

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9200 Corporate Boulevard

Rockville, Maryland

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

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:07 a.m.)

Call to Order

DR. SAMET: Good morning. If everyone could take their seats, we'll go ahead and get started.

I'm Jon Samet, chair of the Tobacco Products Scientific Advisory Committee. Good morning to you all and thank you for being here. I want to make a few statements, and then we will introduce the committee.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act,

we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topics during breaks. Thank you.

Now let me turn to Caryn Cohen.

Conflict of Interest Statement

MS. COHEN: The Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and nonvoting members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug & Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's

meeting, members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the nature and the impact of the use of dissolvable tobacco products on public health, including such use among children. Discussions will include such topics as the composition and characteristics of dissolvable tobacco products, product use, potential health effects, and marketing.

This is a particular matters meeting, during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all committee members to disclose any public statements that they may have made concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach and Mr. Arnold Hamm are participating in this meeting as nonvoting industry representatives acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively. Their role at this meeting is to represent these industries in general and not any particular company.

Dr. Heck is employed by Lorillard Tobacco Company, Dr. Lauterbach is employed by Lauterbach & Associates, LLC, and Mr. Hamm is retired.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with any firms at issue.

I would like to remind everybody present to please silence your cell phones if you have not

already done so. And I would like to identify the FDA press contact, Michelle Bullock.

If you are here, please stand.

Thank you.

Introduction of Committee Members

DR. SAMET: Thank you.

Let's do committee introductions now. Let me check on the phone. Let's see. Mark, are you there, and Arnold?

DR. CLANTON: I am here.

MR. HAMM: And I'm here.

DR. SAMET: Why don't you guys go ahead and do your introductions. Mark?

Mark Clanton, representing pediatrics, public health, and oncology.

DR. SAMET: And Arnold?

MR. HAMM: Arnold Hamm, representing the interests of U.S. tobacco growers.

DR. SAMET: Let's see. You're both quite echoey.

Sherry, why don't we go this way.

DR. EMERY: I'm Sherry Emery from the

University of Illinois at Chicago.

DR. PAMPEL: I'm Fred Pampel from the University of Colorado at Boulder.

DR. HATSUKAMI: I'm Dorothy Hatsukami from the University of Minnesota.

DR. BALSTER: I'm Robert Balster from Virginia Commonwealth University.

DR. HENDERSON: Patricia Nez Henderson, Black Hills Center for American Indian Health.

DR. EISSENBERG: Tom Eissenberg, Virginia Commonwealth University.

DR. BENOWITZ: Neal Benowitz, University of California San Francisco.

DR. SIMONS-MORTON: Bruce Simons-Morton, National Institute of Child Health and Human Development.

DR. PETERS: Ellen Peters, Ohio State University.

DR. DEYTON: Lawrence Deyton, Center for Tobacco Products.

DR. ASHLEY: David Ashley, director of the Office of Science, Center for Tobacco Products.

DR. EVANS: Sarah Evans, Center for Tobacco Products.

DR. PIRARD: Sandrine Pirard, Substance Abuse and Mental Health Services Administration.

DR. MCAFEE: Tim McAfee, director of the Office on Smoking and Health at the CDC.

DR. DJORDJEVIC: Mirjana Djordjevic, National Cancer Institute, representing NIH.

DR. HECK: Dan Heck from the Lorillard Tobacco Company, representing the tobacco manufacturers.

DR. LAUTERBACH: John Lauterbach, Lauterbach & Associates, representing the small business tobacco product manufacturers.

DR. SAMET: Thank you.

We have a busy day ahead, and I think we'll start by hearing from Sarah Evans. Sarah?

Opening Remarks – Sarah Evans

DR. EVANS: Good morning, everyone, and welcome to the second day of the second TPSAC meeting on the topic of dissolvable tobacco products. I am Sarah Evans, and I am the lead scientist on this

effort.

As you know, the information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to aid the committee in its evaluation of the issues and questions referred to the committee.

Today's meeting will consist of presentations and an open public hearing. Presentations will be from FDA. This is information requested from TPSAC on health effects and topography of dissolvable tobacco products, as well as presentations from RTI on an independent review of industry document submissions. We'll also have various invited speakers on dissolvable tobacco products.

It is indeed a full day of presentations, and so to tell you what the topics are, we've broken them down into four parts. After each part, we will have a break.

The first part includes presentations on the health effects of dissolvable tobacco products and

the health effects of long-term use of nicotine replacement therapy.

Part 2 includes chemistry and constituents and analysis of constituents and heavy metals found in dissolvable tobacco products. We'll also hear about the topography of use of dissolvable tobacco products and marketing of dissolvable tobacco products.

Part 3 includes presentations on accidental poisoning from tobacco and dissolvable tobacco products, effects of product packaging, and a summary of the peer-reviewed literature on dissolvable tobacco products.

We'll close with part 4. Part 4 today includes marketing research or marketing practices, behavioral and health effects, and toxicological and physiological effects of dissolvable tobacco products.

I'd be happy to answer any questions.

DR. SAMET: Questions?

[No response.]

DR. SAMET: Thank you. And just a reminder

to the committee that we did hear materials in closed session yesterday that are not for open discussion. So if you will recall that were compartmentalizing our brains in ways they really don't work. But just keep that in mind as we discuss today.

So our first presenter is Dr. Chen, health effects of dissolvable tobacco products.

Presentation – Ii-Lun Chen

DR. CHEN: Good morning. My name is Ii-Lun Chen. I'm a senior medical officer with Office of Science. I'm also an assistant clinical professor at George Washington University Hospital Center. I'm here to talk about the health effects of dissolvable tobacco products from the publicly available literature. And here's the same disclaimer that was just presented earlier.

I'm going to start with the background on the health effects of dissolvable tobacco products and also talk about basic nicotine pharmacology. And then I'm going to have a colleague from CDER talk about their experience with long-term use of nicotine replacement therapy products.

Information available on the health effects of dissolvable tobacco products is typically limited to data on systemic nicotine exposure, biomarker analysis, or intermediate clinical outcomes such as heart rate and blood pressure. Ultimately, we would like to have information on actual organ systemic effects and overall health effects from a particular tobacco product on individual consumers.

Given the limited information available, can we learn from experiences of other oral tobacco and nicotine products to help us understand what health effects may be expected from dissolvable tobacco products?

We do know, for example, that use of traditional smokeless tobacco products such as snuff, chewing tobacco, or snus is linked to cancerous and noncancerous oral cavity disorders, cancers of the esophagus and pancreas, cardiovascular diseases and reproductive problems, and addiction, as mentioned in the 1987 Surgeon General report on smokeless tobacco and in the National Cancer Institute website on smokeless tobacco products.

The Surgeon General report was written prior to development of dissolvable tobacco products. However, it gives us some guidance as to where we might focus our clinical research regarding possible health effects from dissolvables.

Ingredients and characteristics of a specific product are key to understanding its potential toxicity. Tobacco products may be designed to have a number of desired characteristics such as nicotine concentration, pH, and amount of free nicotine or nicotine released into solution characteristics. Thus, the attributes of individual products must be kept in mind when considering the safety both between and within a class of products.

Dissolvables have distinct characteristics from traditional smokeless tobacco products in that they are typically fully-consumed tobacco products, with the oral experience lasting less than 15 to 30 minutes per episode, as compared to other smokeless products that are kept in the oral cavity for prolonged periods of time and then removed.

In the literature, investigators have

provided differing reports on the extent of detrimental oral health effects from use of smokeless tobacco products. A major factor may be that individual smokeless products differ in their content characteristics due to various manufacturing processes as well as their differences in actual use. There could also be confounding factors such as other tobacco product use or alcohol use.

As use of smokeless tobacco products has been associated with several oral manifestations, typically localized to the area of tobacco placement, there is concern that use of dissolvable tobacco may increase risk for oral diseases.

As discussed in the previous slide, dissolvables may be considered a subtype of smokeless tobacco. However, there are likely significant differences, not only in the manner these products are consumed but also differences in manufacturing.

For example, American smokeless products are manufactured differently than Asian or Swedish smokeless products. Even amongst American traditional smokeless products, there are distinct

product classes which are chewing tobacco, moist and dry snuff, and snus. The similarity is that they are all held in the oral cavity between the cheek and gums, but they are distinctly manufactured tobacco products.

Epidemiological studies on American smokeless tobacco use has been associated with low but real risk of oral cancers. The risk of oral cancer from smokeless tobacco use has been mainly attributed to TSNA content, although other constituents likely have a contributing role.

More commonly, use of American smokeless tobacco products are associated with mucosal lesions aside from dysplasia or cancer, including keratosis and periodontal effects such as gingival recession. As some products, such as chewing tobacco, can have a high content of sugar, smokeless tobacco users can be at risk for increased dental cavities.

Furthermore, tooth staining and staining of prosthetic devices such as dentures can occur when smokeless products are used. How the experiences of traditional American smokeless product use on oral

health applies to use of dissolvable tobacco is unknown.

Next we transition to looking at the pharmacology of nicotine. From a 1988 article by Benowitz and others, we can see the change in nicotine exposure over time collected from adult tobacco users administered cigarettes, oral snuff, chewing tobacco, or nicotine gum. The X axis is in minutes, and on the Y axis we have blood nicotine concentration.

Of note, the nicotine content of various products are not the same. The cigarette used was subject's own brand, with nicotine content ranging from 0.8 to 1.3 milligrams. The oral snuff on the right upper corner was American brand Copenhagen or Hawken Wintergreen, with approximately 2.5 milligram nicotine content. Chewing tobacco, which is represented on the lower left here, was mostly Redman, with an average dose of 8 grams, but range was anywhere from 0.9 grams to 17.8 grams. And finally, the Nicorette gum was a 4 milligram dose.

From the Benowitz study, smoking was shown to

produce rapid peaks and troughs of plasma nicotine, whereas using smokeless tobacco products resulted in more sustained levels of nicotine up to one hour. Plasma levels seen with smoking and smokeless tobacco are similar, but blood levels of nicotine fall more slowly after smokeless tobacco or nicotine gum use due to continuing absorption. Total absorbed nicotine from smokeless tobacco was greater than from cigarettes.

I know this is a busy slide, but I'll try to get you through it here.

In the next graphic, also from the same Benowitz study, we can see comparisons in heart rate and blood pressure measurements. These were derived from 10 individuals administered the various products described earlier. For all tables, the X axis represents time in minutes. For the top row, we have heart rate, middle row is systemic blood pressure, and the last row here is diastolic blood pressure.

You can see general immediate increases in heart rate and blood pressure, which normalize over time, but there are variations in cardiovascular

responses among products. At this time, we do not have a well-defined understanding how these differing patterns in blood pressure and heart rate impact cardiovascular health.

Now let's take a look at some of the dissolvable tobacco products available on the market. As you can see, there is a variety in nicotine content among dissolvable tobacco products. The current range is from about half a milligram to 4 milligrams, which is an eightfold range in nicotine content. In comparison, we have Commit nicotine replacement therapy, which come in either 2 or 4 milligrams.

In a 2007 study by Kotlyar and others, 10 adult smokers completed a randomized, within-subject crossover study using five smokeless products over five laboratory sessions. In this graph, we have again time on the X axis and blood nicotine concentration on the Y axis.

Nicotine AUC and Cmax were reported to be highest for Copenhagen snuff. Among the other products, Commit 4-milligram nicotine lozenges had

slightly higher levels of Nicotine than the Ariva or Stonewall lozenges. There are noticeable differences in the nicotine pharmacokinetics among various forms of smokeless tobacco products and nicotine lozenge.

There is another similar study published by Cobb and others in 2010 evaluating six products, which were Ariva, Commit 2-milligram strength, Camel snus, self-selected cigarette, Quest low-nicotine cigarette, and sham cigarette. This study evaluated 28 adult smokers.

In seven separate sessions after overnight abstinence, subjects took one of the mentioned products and were evaluated over several hours. Outcomes such as plasma nicotine, expired carbon monoxide, heart rate, and subject effects were assessed.

In the Cobb study, nicotine levels were reported to vary, as expected, with increases greatest for self-selected cigarette. Non-combustible products delivered nicotine an order of magnitude less than self-selected cigarette.

For heart rate, a significant increase over

time were seen for both the self-selected cigarettes and for the Camel snus. However, no significant increases were observed for Ariva, Commit, or Marlboro snus.

For expired carbon monoxide relative to baseline, carbon monoxide increases for non-sham combustible products -- I'm sorry. Carbon monoxide increased for non-sham combustible products, but no significant changes were noted for the non-combustible products.

From behavioral studies, we know that consumers don't necessarily use a specific product one piece at a time. One might expect that differences among consumers in the amount of product consumed in a single time period, as well as the amount of product consumed over a duration of time, would have differing health effects.

Nicotine delivery, cardiovascular profile, and subjective effects of Ariva, which has 4 milligrams of nicotine, were assessed in a single session by Blank and others. Again, 10 adult smokers were administered Ariva after an overnight cigarette

abstinence. At baseline, subjects were given 1 tablet. Ninety minutes later, they were given 2 tablets, and then another 90 minutes later they were given 3 tablets.

Plasma nicotine was measured, as well as a number of other parameters. In this graphic, we have time on the X axis in minutes; and again, on the Y axis, we have plasma nicotine. And then we can see that the plasma nicotine levels varied according to the number of tablets ingested, with 1 tablet having the lowest level of plasma nicotine and 3 having the most.

Interestingly, the baseline nicotine levels are slightly above 2 nanograms per mL, even though it was after an overnight abstinence. One would expect clearance of nicotine, given that nicotine half-life is 2 to 3 hours. Thus, there were likely some noncompliant subjects in the study.

In this study, the tablets were given in increased amounts every 90 minutes. As the half-life of nicotine is 2 to 3 hours, assessment of dose proportionality may have been better performed if

administration of tablets were done at least 3 to 5 half-lives apart to avoid any carryover of nicotine at baseline.

Heart rate was measured and was reported to increase after tablet administration. However, these increases were independent of dose. Mean heart rate across doses at baseline was 68 beats per minute with a standard deviation of 8, and rose to a maximum of 72 beats per minute with a standard deviation of 7 at 10 minutes post-dose.

In terms of adverse reactions, significant effect of dose in time were reported for nausea, with the scores typically peaking at the 10-minute post-administration time interval. Increased readings were also noted for dizziness, confusion, light-headedness, and nervousness. The total amount of product a consumer may take in one session will likely be limited by dose-dependent side effects, such as nausea.

Later this morning, Dr. Stepanov will be giving a presentation on chemistry and ingredients of dissolvable tobacco products. We don't have an

understanding of the exact correlation between tobacco constituents or biomarker levels, such as TSNA, to clinical outcomes, but it seems logical that less carcinogens and other toxic compounds in a product is desirable.

In 2011, Rainey and colleagues published a study on the chemical composition of Camel dissolvable products. The authors state that the dissolvable tobacco products have the potential to cause mouth diseases, and therefore it is important to understand the chemical composition and potential toxicological effects of some of the ingredients.

Potential health effects from use of dissolvables should not be limited to examining oral health; however, it is useful to understand the full chemical composition of a product. For example, significant amounts of sweetener could have implications for increased dental cavities, as mentioned earlier.

A study published in 2007 by Dr. Mendoza-Baumgart and others evaluated Ariva, Exalt, which is a snus made by Swedish Match, and

4-milligram Commit lozenge, and own-brand cigarette for over a six-week period. In this study, the investigators reported CO levels among Ariva and Commit were similar, as were mean urine cotinine and NNAL levels.

The physiological effects of Ariva were not found to be significantly different from Commit in terms of blood pressure, heart rate, white blood cell, and hemoglobin level. However, the authors cautioned that this is a small pilot study, and that although Ariva use led to levels of total NNAL and cotinine levels, similar to Commit lozenge as compared to approved nicotine replacement therapies, consumers are unaware of other potential toxicants in smokeless tobacco products.

As it will take years of research to develop data and health outcomes from individual products, in the interim it seems appropriate to measure as many known harmful constituents to evaluate the potential impact that a product may have on individual health.

In reviewing the information on dissolvables, it seems that we should not assume that the disease

burden of the various smokeless products are the same, although there may be some overlap. In general, we cannot discount genetic factors which likely play an important role in determining susceptibility to cancers and other diseases from tobacco use.

An area of health that should receive more attention is the effect of dissolvable products on reproductive health, considering women in the wide age range of 18 to 44 years old have a potential to become pregnant. Traditional smokeless products have been used predominately by men, but these new products may appeal to both men and women in that they are more discreet and require no spitting.

In summary, although there may be class-wide health effects from dissolvable tobacco use, there are likely significant differences among individual tobacco products which are in the dissolvable class, which we have yet to define. The overall assessment of a product may be influenced by many factors such as type and amount of tobacco constituents, number of products consumed, product dissolution

characteristics, and use behavior. Additional clinical research as well as development of standardized clinical evaluation processes would help us elucidate the health effects of these products.

I'd like to acknowledge Dr. Elena Mishina, who's the clinical pharmacologist in the Office of Science. And I'd like to invite Dr. Priscilla Callahan-Lyon to present to us the CDER experience evaluating the long-term use of nicotine replacement therapy products.

The CDER experience with NRT is presented to inform us the least health effects we would expect when considering the health effects of dissolvable tobacco products, since dissolvables not only contain nicotine but are processed tobacco products.

Thus, consumption of dissolvable tobacco products would be expected to manifest any long-term safety concerns raised by nicotine replacement therapy products and possible additional concerns from local and systemic exposure to tobacco constituents.

The health evaluation of NRT products should

not be considered sufficient to understand the implication of using dissolvable tobacco products but, rather, a starting point. Thank you.

Presentation – Priscilla Callahan-Lyon

DR. CALLAHAN-LYON: Good morning. I'm Priscilla Callahan. I work at CDER in the Nonprescription Division. And we were asked to discuss the CDER experience for nicotine replacement therapy and our approval process.

Basically, I was given two questions. The first question was what information CDER has for the safety of long-term use of nicotine replacement therapies; and for the purposes of this presentation, "long-term" refers to anything beyond the current labeling on the package. And the second question was any experience or information we have on accidental ingestion or misuse of these products when they became over-the-counter, particularly involving children under age 18.

So to give you a little bit of background, it's important to keep in mind nicotine replacement therapies were approved as drugs, a little bit

different from the way you're doing it here. They are not approved for use by anyone under 18, so anyone using it under 18 years of age is using it off label. They were studied and approved as temporary aids designed to help people quit smoking. And though we do know it occurs, the products were not approved for long-term use.

A little additional background. The original NDA submissions -- new drug application submissions -- included very little nonclinical data other than the published literature for these products. We knew the effects of nicotine. The nicotine replacement therapies were being designed for short-term use, and so smokers could quit. And so the presumption was made that since the NRTs were going to be used for short-term use, it would definitely be less toxic than continuing to smoke, and that the nonclinical data was not needed.

There's very limited data on long-term use of nicotine replacement therapies because they weren't designed for that, and the data are not really adequate comparing the safety of long-term use versus

the safety of not smoking.

I was asked when I gave my practice session to make sure that when I use the words "adverse events" and "serious adverse events," everyone knows what I'm speaking of. So an adverse event, just so you know, is any untoward medical occurrence that's associated with the use of the drug, whether it's considered related to the drug or not. A serious adverse event is one that results in one of those following outcomes, which are pretty obvious, something serious.

Sources of available data. There were several sources of available data that I could look at. I chose to look at three. The first is data that was presented to FDA to support the approval of the product. All of these products were initially approved as a prescription product except for the lozenges.

Then we've looked at the data that was acquired since the products were approved, including data submitted to FDA as postmarketing safety data, as well as safety updates that were submitted when

they were switched from prescription to over-the-counter products.

I also looked at data that was presented at a nicotine replacement therapy workshop we held in October of 2010. Some of the people on your advisory committee were there. I did not look at published literature, the FDA AERS database, and the controlled substance database literature.

So first, the data supporting product approval. The first one was the nicotine gum. It was approved back in 1984. The pivotal study was only for six weeks in a little over a hundred subjects. Supportive study was over a thousand subjects, but again, only six weeks to six months of exposure.

There were no serious treatment-related adverse events. There were a lot of common adverse events, and most of these you'll see in all of these products: nausea, jaw ache, hiccups, insomnia, anorexia. These are things that tend to be associated with excessive nicotine use in any form.

There were four studies, four supportive

studies that specifically looked for cardiac effects, and they did not see any specific cardiac adverse events.

The nicotine gum 4-milligram was approved in 1991. We had a few more subjects here, almost 500 for six weeks in the pivotal study. The supportive study was again about 500 subjects for six weeks. But the drug was available for up to two years for these subjects; however, in reading the data, only five subjects could be documented that used it for the entire two years. There may have been more, but it wasn't particularly well-documented.

There were no serious treatment-related adverse events. The 4-milligram users had more adverse events than the 2-milligram users. We also had a safety review of over 1700 adverse events that were reported between 1984 and 1990 for the 2-milligram gum. There were 68 serious reports and 27 deaths. But this was reviewed by both the reporting physician as well as by FDA, and none of these were thought to be related to the drug product.

There were several nicotine patches approved

between 1991 and 1992, studied in a variety of strengths over 2,000 subjects. The studies, however, were only 12 weeks long. There were no serious treatment-related adverse events in these studies. There were a lot of skin irritation noted, but it was both the active and the placebo, and it seems to be related to the patch and to the adhesive more than to the drug. And then the usual nicotine-related events were noted.

The nicotine nasal spray was approved in prescription form in 1996. Now, this one had a little bit longer. They had subjects that were treated for 3 months at full dose and another 3 months tapering dose, and then there were 241 subjects that had the drug available for up to two years. However, I could not find anything that told me exactly how many people used it for that long.

There were no serious treatment-related adverse events. There was a lot of nasal irritation; this seemed to be noted in almost everyone, and it got better over time, a lot of common adverse events. And there were some nasal ulcers that were noted in

the long-term users. And the other thing of significance on this product is there was a feeling of dependence that was noted in this drug when compared to placebo, about 32 percent versus 13 percent.

The nicotine inhaler was approved in 1997. Again, almost 500 subjects in a similar regimen, three months full dose and three months taper, another 240 subjects in the supportive study. And then there was a couple of supplemental studies that allowed three months of full dosing, and then the drug was available up to 12 months for one and 18 months in the other study. However, smoking was allowed, so that made it little bit more difficult to evaluate this.

There were no serious treatment-related adverse events. There were a lot of flu-like symptoms; that was the most common adverse event in this group of subjects. And then the other adverse events were the ones that you would expect.

The nicotine lozenge. This was approved straight to over-the-counter in 2002. The

2-milligram lozenge has 459 subjects, 4-milligram 450 subjects. They were treated for six weeks, and the drug was available for six months. And about 25 percent of them did use it for six months. Didn't have any serious treatment-related adverse events. The common adverse events were the similar to the others. Hiccups is pretty common in these drugs, for some reason.

Then we had the mini-lozenge, which was approved over-the-counter in 2009. Now, this one they did bioequivalency studies comparing it to the original size lozenge. So there were no new efficacy studies, but they did a pretty good postmarketing safety review of the lozenge and of the gum.

They specifically looked for any evidence of events related to the mouth and the throat, and did not find any unexpected findings. There were some increased reports of nausea and hiccups, but no increase in oral irritation. And there were no serious or unlabeled adverse events in the bioequivalency trials, and the usual common adverse events were noted.

The postmarketing safety review for approval of the lozenge, we had a lot of sources, including AERS that showed that extended use of the nicotine replacement products occurs. It seemed to be a little bit more common in the gum.

Can't really give you any specific numbers, but there were over 30,000 adverse events reports for nicotine polacrilex, which is the active ingredient for the gum and the lozenge. From 2008, only 4 of these 30,000 reports was considered serious, so it's pretty low. The gum and lozenge were well-tolerated. The lozenge seems to have more adverse events that are GI-related, but there were really no unexpected findings in the postmarketing safety review.

I'm going to move now to additional safety data that we've reviewed that were not related to the approval process. These are mostly related for when the products switched to over-the-counter. The gum switched in 1996, and they did an actual use study. Actual use enrollees who quit were followed for up to one year after they completed the study, and somewhere around 5 percent of them were still using

it at six months in spite of the labeling, and somewhere around 3 percent were still using it at 12 months in spite of the labeling.

We also had a post-approval study that was done comparing the abuse liability of the mint gum compared to the original flavor, to smoking, and to d-amphetamine, which is considered the control. And we showed less liability for the mint flavor than the amphetamine, so it was thought that it was not particularly addicting, at least not to that group.

They also had three other studies that evaluated adolescents and the different gum flavors, and found that the gum doesn't seem to be a form of nicotine delivery that adolescents particularly enjoy.

The patches switched over a period of several years between 1996 and 2002, and each time it switched, they did an actual use study. Patients were treated as per the labeling and then followed for up to a year. Most of the time, people quit using the patches after about two months. It doesn't seem to be something that people tend to use long-

term.

They did look at poison control center data. The poison control center data was reviewed at the time of each switch. It consistently showed low levels of abuse and misuse. There were a few reports of accidental misuse in pediatrics and adolescents; most of these effects were very minor. We also did a postmarketing experience looking at residual drug in the patch and whether or not the disposal instructions on the packaging was followed and adequate, and it seemed to be.

The nicotine nasal spray. They did a phase 4 commitment for prescription approval. This was submitted in 2000. They did an abuse evaluation over a one-year period. They didn't see any reports of misuse or abuse. They did a student survey that showed low daily use and limited interest in experimenting with this drug. We also had a poison control center monitoring for it that showed 43 exposures, but no overdoses and no accidental pediatric ingestions.

No evidence of any increased cardiac risk,

and there was a risk of long-term use; a 24-month study that was completed with 18 months of treatment and six months of follow-up that didn't any negative effects on nasal exam and no significant adverse events.

The last bit of information I'll give you is on safety data that was presented at the workshop that we had in October of 2010. Panel 2 of the workshop was given the question, what is known about the long-term safety of nicotine from human studies? And I will tell you that not all of the data that was presented were from long-term studies, but I'll give you the highlights of what we learned.

Dr. Newhouse from the University of Vermont presented a very interesting study. This looked at the effects of the transdermal nicotine on memory. He had 74 subjects; they were all nonsmokers, though some had been former smokers, but none were current smokers. And they all had mild cognitive impairment.

They were randomized to receive the patch or a placebo for six months, and then they were offered the nicotine open label for a six-month extension.

So we had 39 using nicotine for the first phase, 67 who entered the open label, and 54 completed it. The ones who did not complete, most of them dropped out because of progression of their cognitive impairment. It wasn't related to any adverse events.

The drug-related adverse events were very mild to moderate. Very similar between the active and placebo. And of significance, they did not have any withdrawal symptoms when the study ended. Basically, it did show safe long-term use, which was up to a year, in an essentially healthy elderly population with mild cognitive impairment. And for those that are curious, I will tell you that the nicotine did seem to improve the cognitive impairment, or at least kept it from getting any worse, just so you know.

Dr. Robert Murray presented some results from the Vancouver Lung Health Study. This was a very large study in the late '80s, looking at prevention of COPD. There was no randomization of nicotine replacement therapy, and the gum was given free to anyone participating in the study that wanted it and

to any significant others in their household who may have wanted it that were smokers.

In the study, the 65 percent of the smokers who quit used the nicotine replacement therapy. And the gum was the only thing that was available at the time, by the way. At the end of the five-year study, 5 percent of these people were still using the nicotine replacement therapy, about 8 to 10 pieces a day. Some of them were ex-smokers, some of them were smokers, and it didn't really seem to matter. They used it about the same rate.

The original paper for this study described over 3,000 participants using the NRTs, and the adverse events were very minor. Most of them had no symptoms, and a couple of small conclusions that they found. The NRT users had fewer hospitalizations for cardiovascular events than the non-users at the end -- at every year during the point of the study. And they also followed patients that developed lung cancer for an additional seven and a half years, and the NRT risk for lung cancer was not significant, and the risk associated with continued cigarette use

obviously was quite significant.

Then Dr. Joseph presented three studies, small studies. One was a transdermal nicotine in cardiac patients. They had 580 patients that were treated for 10 weeks, and they looked at death, myocardial infarction, angina, arrhythmia, cardiac arrest, and CHF, and they noted similar rates in those that used the patch and those that did not.

There was an observational study, looking at 653 smokers with their first heart attack, and they it looked back to see whether they had used nicotine replacement therapy in the period prior to their MI, and they showed no association.

The third one was a self-control case series that looked at the relative incidence of myocardial infarction, stroke, and death in four 14-day periods, both before and after their first prescription for a nicotine replacement therapy, and they didn't find any evidence of event risk associated with the nicotine replacement therapy.

So in summary, what I can tell you from the CDER experience is that we are aware that long-term

use occurs. The number of subjects that have been exposed in any clinical trial is quite small, and the numbers are not really adequate to support labeling these products as safe for long-term use.

The over-the-counter nicotine replacement therapies, gums and lozenges particularly, don't seem to pose any significant risk of abuse or misuse among adolescents that we can find. We don't know how other formulations would be used. And it's important to note, again, that any use by adolescents in these products is considered off-label, which could be potentially some deterrent. And there's no nicotine replacement product that has a reduce to quit indication available.

Committee Discussion

DR. SAMET: Thank you. And thanks to Dr. Chen.

So we have a lot of time to discuss these presentations and to turn back to our speakers, as needed. I think, remembering that what we would like to be thinking about is what lessons learned are there from this experience that may be applicable to

dissolvable products, I think we should discuss what we heard and perhaps some of what we didn't hear because I think there's maybe some other evidence that is relevant.

So let me open it up for discussion and questions. Sandrine?

DR. PIRARD: It's a question for Dr. Chen. Yesterday we heard from Dr. Rutqvist that the European equivalent, I guess, of FDA decided to remove the warning that snus would be linked to oral cancer because of the lack of evidence.

Now, based on Dr. Chen's presentation, it seems to be a little bit contradictory. So I was wondering if Dr. Chen could comment a little bit more about the association between oral tobacco products and oral cancer.

DR. CHEN: What I can say is that my presentation was limited to presenting the available information on the health effects of dissolvable tobacco products, and so I didn't really look into the epidemiological studies on American snus or other smokeless tobacco use.

So I really can't comment directly on that. But what I can say about the information available on dissolvables is that there just isn't enough information available yet. And, as you know, Star was the first one to come out with the first known dissolvable tobacco products. They coined the term, basically.

In 2001 and 2003, they came out with their two products, Ariva and Stonewall. Then only more recently, in 2009, did RJR start test-marketing the Camel line of products, the dissolvable orbs, sticks, strips.

So there just isn't enough information to make any sort of decision on that point. But it'll be interesting over time, the evidence that evolves, and take it from there.

DR. SAMET: Other questions? I may force a little discussion here, I think.

John?

DR. LAUTERBACH: I have a question for Dr. Lyon. At what point in time did the FDA permit flavor advertising on the package of NRTs such as

terms such as "fruit chill," "coated for bold flavor"? And has any abuse liability been done since those labelings were allowed?

DR. CALLAHAN-LYON: To answer your question, I don't know when those were allowed. I didn't look at that. And abuse liability studies for that would go through a different section of FDA than us. So I don't know the answer to your question.

DR. SAMET: Let's see. Ellen?

DR. PETERS: I have a slightly different question and am wondering if you have any data on this. The health effects that both of you spoke about had to do with the health effects of the products as they were used. But that use matters, and it's linked to perceptions of the risks and the benefits of using that product. And I'm curious what you know about what people perceive as the risks of the products and what people perceive as the benefits of the products, in particular.

So, for example, I can imagine that the perception of some of the physiological effects, the dizziness, the confusion, light-headedness, and

nervousness -- I'm reading off something from the Blank study -- those would be negative for me. They may be positive for other people, for adolescents, perhaps, for other sensation-seekers, maybe. I don't know what the answer is.

The abuse liability potential and other effects depend on these perceptions of the risks and benefits, not just what the actual health effects are as used, because if people don't use it, it doesn't exist. If people overuse it, something else might exist than using it as recommended.

DR. CALLAHAN-LYON: I understand what you're saying. I don't know that we have any information that specifically looks at that.

DR. CHEN: Later on today, Sarah Evans is going to talk about the topography and use behavior. But as far as I saw in terms of health effects, again, I didn't have any studies that I could point to, to give you information and answer that question.

DR. SAMET: Dan?

DR. HECK: Yes. Dr. Lyons, I noted your last slide, the last bullet, indicated that there's no

formal indication for use to reduce, what we I guess would term yesterday dual use of NRT and perhaps the occasional smoker.

Do you have any sense from your reading of the literature just what percentage of NRT users may in fact use NRT as an adjunct or as a way to cut down their smoking with parallel use of NRT and the occasional cigarette?

DR. CALLAHAN-LYON: No. There's no controlled study on that that would give me a definite sense. No.

DR. SAMET: Sarah?

DR. EVANS: Dr. Callahan-Lyon, could I just make clear that if it's something like dual use that's off-label use, then the FDA would have no data on that?

DR. CALLAHAN-LYON: That is correct.

DR. SAMET: Bob?

DR. BALSTER: I know I know the answer to this. But just to be really clear, are there any contraindications at all for the use of any of the NRT products except for being under the age of 18?

DR. CALLAHAN-LYON: There are labeled things for which we do not recommend, and there's warnings. And one of the contraindications that's listed on the labeling is use of any other nicotine product.

DR. SAMET: Just a clarifying question. Then, actually, what I'd like to do is circle back through what we heard and talk, really, in a little bit more detail about potential cardiovascular effects, the oral health issues, and I think we should talk about cancer, and I think we should be a little more systemic.

But Dr. Chen, I want to go back. You have what I would say is a somewhat generic slide where you say, understanding health effects is complex. I think we will all agree. But I just want to go back to the slide and make sure I understand what you're saying because I'm not sure these remarks should be interpreted too broadly.

So you say the disease burden of the various ST products are not necessarily the same. I'm not sure we have evidence one way or another on that except for the oral cancers. Can you bring some

specificity to this?

Then when you talk about genetic factors, actually, in terms of the genetics of disease risk associated with smoking, the only really strongly linked genetic factor so far, to my knowledge, is alpha-1 antitrypsin deficiency. There are many genes that have been explored, some interesting possibilities.

But let's just try and be a little more specific about your comments on those two points.

DR. CHEN: Sure. I wish I could be more concrete. But as you know, the literature on dissolvable tobaccos, specific to dissolvables, is limited to maybe 30 articles or less. And just looking over these articles, it's quite apparent --

DR. SAMET: Your comment actually was the disease burden of the various ST products.

DR. CHEN: Smokeless tobacco products. Right.

DR. SAMET: They're not necessarily the same, so --

DR. CHEN: Right. And considering that

dissolvable tobacco products may be a sub-class of smokeless tobacco products. And just looking at, for example, from Dr. Benowitz's article, there are comparisons of cigarette products and snus or snuff products, and then as well as in other articles, comparing available dissolvable tobacco products.

Looking at them, you see that the manufacturing may be different. The content may be different. And so we don't have any information to exactly correlate the different characteristics of products and then the ultimate health outcomes. So we have a hard time understanding. Just because they're the same product class or under a group of products -- they're smokeless tobacco products, or they're even within the same dissolvables -- we can't assume that the health effects are the same.

So what I really meant to say, I think, is that we really should be looking at products one at a time and not necessarily just assume that just because they're in one class of products, that all the health characteristics or health effects will be the same for them.

DR. SAMET: Then, again, just to make sure we can bring some specificity. On the point of genetics, actually, around smokeless tobacco use, I'm not sure we have any information.

DR. CHEN: Again -- yes, we don't. And it's just that we have to keep in mind that not every human person is the same, and that there are other factors other than just constituents and characteristics of a product, and that the individual needs to be considered.

DR. SAMET: Thank you.

So why don't we go back to the cardiovascular consequences. We heard a little bit, I think -- probably particularly from your work, Neal -- about some of the well-documented short-term consequences of nicotine administration, and then some longer-term data, albeit from somewhat small populations, where there's some longer-term information from the FDA presentation.

So perhaps, Neal, can I draw you into the discussion? It's now 6:00 a.m. in San Francisco, so --

[Laughter.]

DR. BENOWITZ: Sure. I comment first, before we talk about the cardiovascular effects of nicotine, that there are some dose-response issues. And the dissolvable products that we've looked at so far in terms of kinetics had relatively low nicotine concentrations. The NRT that we studied in cigarette smoking produced higher nicotine levels, in general. So it's problematic extrapolating. We just don't know about lower doses.

We certainly know that nicotine has got the potential to have adverse cardiovascular effects. One can look easily at heart rate and blood pressure, but there are some studies in cigarette smokers, and I think nicotine gum, showing that in certain situations, you can see coronary vasoconstriction.

There are studies that show nicotine can produce endothelial dysfunction, so it can impair dilation of blood vessels. There are studies suggesting that nicotine can have adverse effects on glucose tolerance, and so people who are diabetic could be worse. And smoking itself is a risk factor

for type 2 diabetes, and conceivably nicotine could play a role.

There are certainly concerns about reproduction. You have potential adverse effects of nicotine on various reproductive processes. And there are also some concerns in very specialized test systems about effects of nicotine on apoptosis, so basically inhibiting the self-destruction of cancer cells.

So while there are some theoretical concerns, though, the problem with evaluating nicotine in existing data is that nicotine is used by tobacco smokers. And the risks of nicotine, if there are some, are very small compared to tobacco. So the risks of tobacco dwarf anything from nicotine. So any time you switch someone from tobacco to nicotine, it's almost impossible to pick up a risk because their background from tobacco is so much greater.

So unless we had data on people who are primary nicotine users without combusted tobacco, we couldn't really answer the question. And I think that's why the snus data is really the only thing we

have to look at for long-term nicotine exposure. And the snus data -- again, I could go back to what Dr. Chen said. Smokeless tobacco really can't be generalized. There are so many different forms around the world. So if you look at studies that have tried to pool smokeless tobacco from all around the world, it does look like there's a cardiovascular risk. But if you look at Swedish snus, the cardiovascular risk data are much more modest, if any. And that's the cleanest product, as far as I know.

So it's hard to say. There certainly is the potential that nicotine could have adverse effects. But I'm personally not aware of any convincing data on just pure nicotine use suggesting that there are adverse cardiovascular events.

DR. SAMET: And we had -- of course, you weren't here yesterday, but we had extensive discussion about the Swedish experience, and we can fill you in about that.

So your comments -- we've heard about some of the data from the short-term administration and the

acute effects of nicotine administration, and then one window on potential longer-term consequences from the trials that were mentioned. But those are relatively limited in terms of the numbers of participants in trying to pick up a longer-term cardiovascular risk.

So I just want to complete the discussion by getting your read on the potential sources of information on any longer-term cardiovascular risks of nicotine administration alone, which would have to be then generalized back to the dissolvables as that we don't have very much information beyond the Swedish experience; perhaps the relatively short-term follow-ups that we've heard about in these various clinical trials.

I don't know if you have other data sources to bring forward.

DR. BENOWITZ: No. So far as I know, there are no other data sets where people have been exposed to substantial amounts of nicotine of long periods of time other than smokeless tobacco in nonsmokers. There just isn't enough data for people who have,

say, quit cigarette smoking and used NRT for a long period of time.

DR. SAMET: Other comments on the cardiovascular? Mark? Arnold?

DR. CLANTON: Yes. This is Mark. I just have a comment.

MR. HAMM: No comments from me, Dr. Samet.

DR. SAMET: Thank you. Mark?

DR. CLANTON: Yes. My comment has to do with a focus on looking at elevated blood pressure across the population. Now we have initiatives to reduce salt across the board, dietary salt, in an effort to reduce blood pressure and hypertension.

So although we can continue to talk about no adverse events, which in this case defines coronary -- (audio gap).

DR. SAMET: Okay. We're having a little trouble hearing you. But I think I got the gist of it.

Let's see. Mark, are you using the speakerphone?

[No response.]

DR. SAMET: He's gone.

Mark, are you gone?

DR. CLANTON: No. I'm not gone. I'm using a microphone and not a speakerphone.

DR. SAMET: You sounded a little better than before. Why don't you say it again.

DR. CLANTON: I'll hold my question till it seems better. Thank you.

DR. SAMET: Okay. Dorothy?

DR. HATSUKAMI: I think one area that we need to concern ourselves with is the whole issue of dual use because it appears that there's dual use of -- potentially dual use of dissolvables with cigarettes.

So the question I have is actually to Dr. Lyons, is there information at the FDA regarding the dual use of nicotine replacements with cigarette smoking and the safety of doing that?

DR. CALLAHAN-LYON: Well, the information is pretty limited. That would be considered off-label use. We do have some information. Most of it, I think, would be -- the most useful body of

information would be in these reviews that were done at the times when the products switched from prescription to over-the-counter, and we could look at the AERS database, and we could look at people that reported an adverse event and the numbers that said that they were using the products either longer than they should have or while they were smoking.

There are a lot of reports. The problem with looking at anything in the AERS database, the adverse event reporting system to FDA, is that you have no denominator. So you have no way of doing any sort of evaluation of the commonality of something. We only know the positives. We don't know how many negatives there are.

So we know from a lot of these studies, from anything in the literature, anything in the lay press and anywhere else, that there are a lot of people that use the products in dual use. We know it happens. But how common it is and how associated that is with adverse events and problems, we have no way of knowing.

DR. SAMET: Neal?

DR. BENOWITZ: There certainly is an experimental database looking at the use of NRT for nicotine reduction studies. Dorothy has done some other stuff as well. And those studies have not shown, as far as I know, any cardiovascular risk. So when you give people nicotine and you try to help them reduce smoking, there has not been evidence of risk that I have seen.

DR. HATSUKAMI: I want to add to that. Anne Joseph did do a study looking at the reduction of cigarette intake using NRT among people who have had a history of cardiovascular disease, and we didn't see an increase in terms of cardiovascular events happening within that population among those who were given nicotine replacements with cigarettes.

DR. SAMET: Bruce?

DR. SIMONS-MORTON: Yes. I was wondering. There's no information about NRT use among pregnant women?

DR. BENOWITZ: There are data. There have been several studies that have been done, and there clearly are physiological effects. Whether there are

adverse effects is unclear. Some studies have had a signal, but they were confounded with group differences on entry in the trial.

The problem with those studies is that it hasn't been very effective to have people quit smoking. So it's hard to look at any risk of NRT by itself if the people are still smoking. So I don't think we have definitive data. There are data with smokeless tobacco and pregnancy suggesting that it is harmful. So I think nicotine does have the potential to have adverse effects in pregnancy.

DR. SAMET: Neal, just to finish the discussion of pregnancy, the animal studies from Duke -- is it Slotkin and the effects on the fetus of nicotine administration in rat studies?

DR. BENOWITZ: Well, there are lots of data suggesting that if you give a pregnant animal nicotine, that there are permanent neurological changes in the fetus, and there are neurobehavioral changes that persist after birth. But that's probably true with a lot of psychoactive drugs in general.

But clearly, I think if nicotine can be avoided in pregnancy, that would be good. And I think any decision about any kind of tobacco products should exclude pregnancy.

DR. SAMET: Dan?

DR. HECK: Just to the topic a moment ago about the dual use and potential effects or exacerbation of cardiovascular symptoms, there may be such data from the NIDA studies at Duke. Dr. Rose -- because I know in some of the recent protocols, they've been looking at placing cessation subjects on NRT in advance of the date, the target quit date for smoking. So there may be some cardiovascular information, at least on a short-term basis, from those recent studies.

DR. SAMET: Thank you.

Other comments? We've talked about cardiovascular disease. We've had some discussion about reproductive outcomes and effects on the fetus. Let's just go to cancer, where I think there are probably two sets of concerns. One is oral cancer and other oral health effects, and then this general

concern about cancer.

Neal mentioned briefly in vitro studies that show inhibition of apoptosis by nicotine administration. And I think -- I haven't looked at this for a while -- but there have been four or five studies in different systems, I think; maybe you can give an update. I can't say I'm tracking it But that's raised general concerns about cancer risk.

DR. BENOWITZ: Yes. There are studies in isolated animal systems, not necessarily in intact animals. But when you said models of apoptosis, nicotine can inhibit that, and that's thought to be an important defense against cancer, basically killing off cancerous cells.

So there has been concern about that. And there's also been concern that nicotine could contribute to cancer not because it really causes any cancer, but when other constituents of tobacco initiate cancer, it impairs the body's defense. So that's been a concern.

So there are some concerns, theoretical concerns, that if someone is a former smoker and

their cancers have been activated and they continue with NRT for a long period of time, it could increase cancer risk.

There was one study that was part of the cancer prevention study that suggested that people who were former smokers but switched to smokeless tobacco -- and this is not modern; this was all to smokeless tobacco -- had an increased risk of lung cancer. It is one study that showed that; not the Swedish studies.

In trying to figure out why that might be, the only explanation I could think of is that if you already have sort of nascent lung cancer and then you take nicotine for a lung period of time, it may impair your ability to control it.

Again, I think nicotine and cancer, the only pure data with the cleanest product comes from Sweden. And there, to my knowledge, the main risks of concern have been pancreatic cancer, with a small increase in risk, but no evidence of other kinds of cancer.

DR. SAMET: All right. And we heard about

that experience at some length yesterday.

I guess the other question -- and I think we've heard now, yesterday, some discussion about the oral health consequences of smokeless tobacco products in general, some more discussion today. And I guess another issue well beyond my expertise is the extent to which these studies of different products are informative about the potential oral health risks of dissolvable products.

I think that's worth -- that's something we have to think about. I don't know if anybody on the committee has some thoughts about that. Looking around the table, we're not necessarily a group of oral health experts, but Dan is.

DR. HECK: Just some general thoughts on that, Mr. Chairman. We did indeed hear some about the Swedish experience yesterday. But as I think some of us are aware, there is a wealth of additional information that was not brought up yesterday.

The numerous various expert panels including the NCI and the senior group recently -- there's a lot of thoughtful analysis into the Swedish datasets

that are already on the books, and we only scratched the surface of that yesterday. I know Dr. Curtin's presentation in the prior meeting cited another few dozen, perhaps, of additional studies. So there's a lot of primary information.

To agree with Dr. Chen and I think some others' cautionary notes today, it really is important to discriminate the type of smokeless product that's being described in, let's say, an epidemiology study. Some of the early studies were deficient in that respect, where there wasn't discrimination between loose leaf chew, traditional moist smokeless products, and certainly some of the newer products.

In terms of the extrapolation of the Swedish experience to the dissolvable category here, I think we do have -- one fact that I think is in favor of examining the Swedish experience is the similarity of the type of tobaccos generally going into these products. The very low nitrosamine curing process that I think we're generally familiar with, used in the snus process, is very similar to the type of

tobaccos used in these dissolvables, as far as I'm aware to date. So I think that does suggest to us that we can get some value from the Swedish experience.

DR. SAMET: Tim?

DR. MCAFEE: I just want to again come back to a point that there really are two issues associated with this. And the one that we're going to tend to focus on is probably the specific characteristics of the dissolvables around their direct effects, whether it's carcinogenic or cardiovascular, with the hypothesis that people just looking at the effects that that product would have on the assumption that people are only using that product.

But we certainly know -- and this is one of the concerns about the extrapolation of the Swedish experience to the U.S. -- that in the U.S. for smokeless products in general, and it looks like for dissolvables probably as well, based on our surveillance data, that the majority of people that are using smokeless products, particularly in terms

of -- if anything, of trends, in terms of young people, that we are not looking at the historic assumption of what would happen with cowboys in Wyoming, where they're only using a smokeless product. The majority of people are engaging in dual use, and if anything, the trend is more in that direction.

So in some ways, it's potentially almost -- again, looking at the population effects, almost an uninteresting or -- it's a less important question what the isolated impact of using a dissolvable is, even if its cancer risk, its cardiovascular risk is low, unless we can also get over the hurdle of what the impact of more widespread marketing uptick, et cetera, would be.

We have the danger that we would ultimately end up with more people smoking, and that we think that the benefits of getting people to smoke a bit less because they're using a dissolvable or using a smokeless product are probably pretty minimal at the population level.

We know from our data just even looking at

the secondhand smoke exposure that it takes relatively low levels of exposure to combustible tobacco smoke, whether it's secondhand or whether it's directly inhaled, to have significant effects on cardiovascular health. And probably, in people that have been smoking for a long time, there's evidence from some of the Scandinavian large cohort studies that cutting back on smoking is not going to give us as big a bang for the buck as we might have thought a decade ago.

So I think, again, it's still important to look at the independent cardiovascular and cancer risks associated with dissolvables, but we can't lose track of the fact that we have to understand what the actual patterns of use would be.

DR. SAMET: We had an interesting discussion yesterday about the extrapolation of the Swedish experience to the U.S., and decided that we had to do any generalization very cautiously, if at all.

I think one point that we saw out of the Swedish experience was that, over time, the use of products changed such that there was now a

substantial pull. If I remember right, 50 percent of the users were using snus exclusively and not mixed with cigarettes. And there had been a switch as new users came on who used snus alone.

So I think, if there is one lesson there, there could be some temporal dynamics in use of these products, depending on what is happening in the nicotine marketplace, I suppose. But I think your point is well-taken in terms of dealing where we are now.

Bob?

DR. BALSTER: There's one other area of research that's not been mentioned that I want to just briefly bring up, and that is the potential of long-term neural behavioral effects of youthful nicotine exposure. There's fairly significant published literature on this.

Of course, there's always been a concern about the role of tobacco's use in general and smoking particularly as sort of a prodrome to other forms of substance abuse. And one of the key areas of research has been looking for a mechanism that

might account for that, or a causative mechanism by which nicotine could do that.

So there's been quite a large number of studies exposing youthful animals, rats primarily, to nicotine and looking at both behavioral and nervous system effects. And there's no question that perinatal exposure, adolescent exposure, can produce changes in such things as gene expression, can produce changes in brain neurochemistry, can produce changes in behavior of adult organisms, can produce changes in evidence for susceptibility to the reinforcing effects of other drugs of abuse.

So there's a fairly significant literature on that area, and the direct causative role of nicotine in any type of predisposition to substance abuse or any other behavioral problem is not definitively known. But I think it's something that we need to be aware of with nicotine. It would of course apply to nicotine in any form.

DR. SAMET: Let me check with Mark and Arnold. Anything?

DR. CLANTON: Nothing here.

MR. HAMM: Nothing here, either.

DR. SAMET: Thank you.

Then I think one thing we might do at this point is have a reminder about our questions to the committee. And these are questions that we are to use to help us develop our ultimate report on our dissolvable charge. We looked yesterday at number 1, but number 1 is followed by 12 more questions.

[Laughter.]

DR. SAMET: There's a few relevant to what we just heard. And we've got a few minutes; maybe we could just sort of flash them by and just remind everybody, because we're going to hear a lot of materials today relevant to these questions.

So we have this peer-reviewed literature, this set of 23, 24 papers. And then why don't we just continue on, Caryn.

Surveillance, poison events, initiation; youth perceptions, we'll hear more about this later; adult perceptions; dual use, which we've already begun to discuss; abuse liability; cessation.

Okay. Continue on.

We've been at this point dealing with health effects. Here's a question about morbidity and mortality; toxicity, marketing, and public health impact, which our question is about impact in the Act that we need to address.

So I recognize that for some of these, there are no data, and there are not necessarily answers. But highlighting uncertainties could also point to where research is needed or surveillance. So I wanted to offer this reminder of the reach of what we have to consider, beginning yesterday and continuing today and then tomorrow, as we come back and talk about where the evidence stands on these questions.

So I don't think we need to launch into a lengthy discussion of them now, but just in terms of closing out this session, let me just see if there are any more questions relevant to our presentations.

Yes, Patricia?

DR. HENDERSON: I just have a question about the role of obesity. I'm not sure what the obesity rate is in Sweden, but here in the United States, of course that's an issue and how that plays in the

morbidity and mortality with dissolvables. I'm just throwing it out there.

DR. SAMET: So keep hold of it, and we'll come back to it.

Neal?

DR. BENOWITZ: I'd just follow up. You asked some questions about genetics. And for smoking, we actually have some pretty good data on the alpha-3, alpha-5, beta-4 gene complex and a variety of smoking diseases, and also the cytochrome P450 2A6 gene and lung cancer.

We don't have it for smokeless tobacco because there's not enough disease so far. But in a study which is not published, we found some very interesting data in some Alaskan natives that the rate of nicotine metabolism in smokeless tobacco users involves carcinogen exposures, and people who are fast metabolizers get exposed to more carcinogens.

So there are conceivably some genetic factors that play a role in smokeless tobacco broadly. I'm not sure how that relates to dissolvables. But there

are some potential genetic moderators that could be looked at.

DR. SAMET: Right, and obviously, a huge amount of work going on. When I commented earlier, I think my main point was to clarify -- I think, in fact, the word was "may prove important." Well, these may prove important. I think there's a lot of work still to be done to understand how they may play out at both the individual level and the population level.

So I think we are up to break time. And I think I need to offer you the reminder to not discuss things during the break.

That's it. So a 15-minute break.

(Whereupon, a recess was taken.)

DR. SAMET: So I have two important announcements. Committee members, remember that you need to turn in your lunch order. And we actually have a lack of chairs; there are people sitting outside. So if people could make sure to not use two chairs by sitting in one and putting your coat on the other, then we'd have more chairs available, please.

Thank you.

So we're going to move on and next hear from Dr. Stepanov from the University of Minnesota, Toxic and Carcinogenic Constituents in Dissolvable Tobacco Products. Thank you.

Presentation - Irina Stepanov

DR. STEPANOV: First of all, thank you for inviting me to give this presentation. And I will talk about some results of the analysis of toxic and carcinogenic compounds in dissolvable tobacco products.

Now, I don't mean to insult anyone's intelligence. I know, because of the really narrow focus of these meetings, I will probably repeat what was said before or will say things that everybody knows anyway.

So dissolvable tobacco products have been introduced more than a decade ago. It started with Ariva and Stonewall, produced by Star Scientific. And then in 2008, RJR came up with this line of dissolvable Camel products that include Camel sticks, strips, and orbs. And originally, these products

came in two flavors, Fresh and Mellow. And eventually, they were substituted with this new version of products that are still sticks, strips, and orbs, only now is just single flavor. And in 2011, Marlboro and Skoal sticks appeared on the market.

So we received all these products as a part of one of our ongoing projects and analyzed for a range of constituents that are considered to be important for smokeless tobacco products.

Before I move on to, actually, chemical composition, I would like to very simplistically summarize what are the major concerns out there related to the use of these dissolvable products. And because this is tobacco, of course, first of all, what comes to mind is toxicity and carcinogenicity and addictiveness.

In terms of toxicity and carcinogenicity, there are researchers who are concerned about chronic exposure to whatever it is in these products in adult users. There is also concern about accidental poisoning in children. In terms of addictiveness,

there is a concern about sustained tobacco use in current smokers and addiction. I should have added initiation, addiction, and graduation in new tobacco users who are -- graduation means moving on to products that have higher nicotine content or to a more efficient nicotine delivery device such as cigarettes.

All these outcomes are influenced by a number of factors such as -- these are not all the factors, but major. That would be chemical composition of products themselves plus individual characteristics of people who use these products such as, for example, genetic makeup that defines a response to toxic and carcinogenic effects present in tobacco products, as well as behavioral aspects, how these products are used. And I will focus today only on chemical composition as an isolated factor.

This is the list of analytes that I will present today. As I said, it's not comprehensive. We have some more data on other constituents. But I will talk about tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, nicotine pH,

unprotonated nicotine, and moisture content and portion weight.

We'll start with tobacco-specific nitrosamines, which are considered one of the most important group of carcinogens in both unburned tobacco and cigarette smoke. Among seven TSNAs that have been identified in tobacco and cigarette smoke, these two, NNN and NNK, are the most important due to their high carcinogenicity and also abundance in most tobacco products.

In laboratory animals, NNN causes esophageal cancer. NNK causes lung and pancreatic cancer. And the mixture of two causes oral tumors. And there were two recent studies in smokers in the prospective cohort that showed a strong, significant relation between exposure to NNN and NNK and the risk of development of lung and esophageal cancer in smokers. Based on all the available evidence, NNN and NNK are classified as human carcinogens. So this is a very important group of constituents.

We analyzed these tobacco-specific nitrosamines in other products that I showed on the

first slide. And first, I just wanted to point that I kind of color-coded -- hoping it will be helpful -- products of different flavors but the same brand; for example Ariva, different flavors. Here is Stonewall, Camel orbs, and so on. These are Marlboro sticks and Skoal sticks.

One thing that you can see without reading actual labels is that there is a really wide range of TSNA content among these products. So I guess the major message here is that even though these products have kind of earned the reputation of being low nitrosamine products, they are not all the same.

So these newer Marlboro and Skoal sticks, they contain up to 3 and a half micrograms of NNN plus NNK, which are known human carcinogens per gram dry weight. So these are results per gram dry weight. Well, these products are by no means low in nitrosamine at this point.

Another detail that I wanted to focus on is this difference, for example, in Camel orbs. This is the original version, Mellow and Fresh, and this is the new mint-flavored orbs. You see the difference

in TSNA levels; the same for strips. However, for sticks, levels are the same. So I pulled out data numbers just for this subset of products.

This table includes, actually, a version -- I thought it will be easier to visualize what kind of version of product this is; portion weight, moisture content, and NNN and NNK separately, all these per gram dry weight.

Let's just go one by one. If you look at orbs, you can see here this newer version has about the same amount of NNN, relatively low. Well, it's slightly higher than in the original version, but one who does an analytical chemistry kind of analysis, this is not a significant difference, actually, in the numbers.

But if you look at NNK, for some reason the level of NNK is much higher in this new version compared to what we've seen before. I don't know what the reason is, whether a different tobacco type was used or a different manufacturing, some kind of detail, but it translates into more than a twofold increase in NNN plus NNK in this newer version.

Now, if you move to strips, the levels of NNN in this new version are slightly higher as well. I would say in this case it is higher. And levels of NNK again are higher than in the original version, which leads to a more than twofold difference between original and year one. And also, moisture content decreased and portion size actually increased. So now these strips, they are visibly actually thicker and dryer than the original version.

In case of sticks, not much actually changed. You can see that levels of NNN and NNK are even slightly lower here in the new version. And so the levels per gram dry weight didn't change.

Now, these are results per gram dry weight, which is important in terms of manufacturing approach or type of tobacco used for comparison among the products. However, if you think about actual exposure of consumers, you want to see how much is present in a single dose.

So these are results, the same numbers for the same products, only expressed in amounts in single portions. And again, you see pretty much the

same breakdown, a large variation among products. It is quite low here in Ariva.

Now you see difference, actually, between Ariva and Stonewall, even though levels of nitrosamines are quite similar in per gram dry weight. But because of the difference in portion size, you get a little bit more in single tablet of Stonewall compared to Ariva. And ranges go up to -- let's see, .7 micrograms of NNN plus NNK per single portion of Skoal stick.

So now imagine using a few sticks over the course of the day. A person would be exposed to a few micrograms of these known human carcinogens. So this is something to consider.

Now I will move to polycyclic aromatic hydrocarbons, which are known environmental contaminants with benzo(a)pyrene being a representative carcinogenic PAH. And this is a really wide range of chemicals that exhibit a wide range of toxic effects in different organ systems. Some of them are carcinogenic.

We are interested in this group of compounds

because we found that relatively high levels of PAH are present in U.S. moist snuff, which is probably happening during tobacco processing, so it's contamination coming from fire-curing.

So in our previous studies, we showed that products like Camel snus or Marlboro snus are relatively low -- very low, actually -- in PAH content. But it makes sense to keep an eye on this group of compounds.

So this table summarizes levels, again, per gram dry weight for these products. And I didn't show the different flavors; I just summarized. These are levels of BaP that are actually very low. And the sum of 8 carcinogenic PAH -- I should have provided a reference. So this line, A, refers to carcinogenic 8 TSNA and a total of 17.

We actually have method for analyzing 23 different PAH in single sample in single analysis. But because levels generally are so low, we detected only 17. And amounts are not really significant compared to other sources of exposure to these carcinogens. And if you look at amounts for single

portion, levels are even lower. There are just a few nanogram of total 17 PAH in single portion.

Now, moving to nicotine, which is probably the most important constituent because it is the major known addictive component of tobacco. And this is why people do use tobacco products, eventually getting exposed to all the toxic and carcinogenic compounds -- I'm talking in general -- in I guess highly contaminated products in cigarette smoke that leads to devastating health effects. And then if people want to quit, they can't because there is nicotine there. So it's like a vicious cycle, with nicotine indirectly causing negative health effects. But on its own, it's not carcinogenic.

Here I'm actually referring to Neal's work. Nicotine itself has been shown to be associated with fetal toxicity. Well, there was a conversation earlier that it is more in animal studies, and some association with cardiovascular risk factors.

Nicotine that is present in unprotonated form more easily crosses cellular membranes than protonated nicotine, and that's why it's considered a

biologically available form. This is the form that gets really quick in the blood and reaches the brain. And the amount of nicotine that is present in unprotonated form depends on product pH.

So this table summarizes levels of nicotine in these dissolvable products. And generally, again, this is per gram dry weight at this point. Generally, these products are relatively low in nicotine content. You can see as low as 3 milligrams per gram tobacco, for example, in orbs and strips, up to 7 in the Marlboro sticks; while in some other -- like in cigarette tobacco, it can be over 20 milligrams per gram.

pH levels seemingly do not really vary much. It seems like there is not a lot of variation, but actually, even the slightest changes in pH cause drastic changes in unprotonated nicotine content. So if you look at this column here, this slight difference in pH actually leads to a range from here, 6, to close to 60 percent of nicotine being in unprotonated form. So there's a tenfold variation.

Looking at unprotonated nicotine expressed in

milligrams per gram dry weight, again, levels ranged from very low here in these two products to, actually, up to 3 milligrams per gram dry weight in Marlboro sticks.

This is kind of interesting, that in the case of Camel and Marlboro snus, we see a higher level of unprotonated nicotine in Camel snus than in Marlboro. But in this case, when you look just at results per dry weight, unprotonated nicotine seems to be higher in Marlboro than in Camel.

Now, these are the amounts of total nicotine per single portion. Again, these numbers take into account moisture content and portion size, so you see all this variation among products. Actually, now, because of the differences in portion size, this relationship between Camel sticks and Marlboro sticks goes back to what is seen in snus products. The exposure from Camel would be higher than from Marlboro.

These are levels of unprotonated nicotine. So the whole distribution completely changes, which is not surprising because there is not much

necessarily correlation between total nicotine and unprotonated nicotine. And in this case, we have Camel sticks actually having the highest amount of unprotonated nicotine per single portion.

Another detail that I wanted to point out is that products that are offered by one manufacturer, they seem to offer a gradient of unprotonated nicotine levels across products. For example -- well, let me move to the next slide here. I pulled out results for Ariva versus Stonewall, so you can see there is about a threefold difference in unprotonated nicotine between these two products. In the case of Camel dissolvable products, again you have this flexibility of unprotonated nicotine levels among products.

When I looked at these, I couldn't help but think back about this publication by Greg Connolly where it seems like this was used in the past as actually in product development, where products with lower nicotine, unprotonated nicotine levels were marketed mostly to people who start, begin using smokeless tobacco. And then when tolerance is

developed, people move up to higher nicotine-containing products. And eventually, sooner or later, it's Copenhagen.

Now, I don't want to state that this was actually deliberately designed with this scheme in mind, but the graduation process itself has been shown to work in the past, and still works with conventional products. So there is this possibility of consumers themselves actually graduating to higher levels, and then moving on to maybe conventional products. Just theoretically, it is possible, based on the chemical analysis.

To summarize, we saw a wide range of nitrosamines among different brands and products. In addition, we also found some variation in nitrosamine levels within the same product as it is being modified, coming up with new versions, and very low levels of polycyclic aromatic hydrocarbons. This is still true.

We also see a larger variation in unprotonated nicotine levels in total nicotine, which is again not surprising. This is what is commonly

seen in conventional products.

Just going back to this scheme that I started with, just to summarize, chemical composition, as an isolated factor, does it support or how does it refer to these concerns? So in case of chronic exposures to constituents present in these products at this point in time, we found that there is up to .7 micrograms of NNN plus NNK that are potent carcinogens, present in single portions. So it might translate into a few micrograms of these carcinogens per day. And eventually, this kind of exposure can be dangerous.

So I think that it does support -- chemical analysis, chemical data, does support this concern. So this is something that has to be looked at.

Children, accidental poisoning, again, forget about containers being childproof. I actually know that, especially, the first version was researcher-proof.

[Laughter.]

DR. STEPANOV: I had people in the lab coming to my office and asking to help to open them. I

think that the newer version is a little bit easier to open, but still, just thinking about chemical composition, there is up to 3 milligrams of nicotine in a single portion of some products, and as much as 1 milligram is enough to induce severe toxicity in children. So in theory, yes, there is a concern. It is justified.

Addictiveness, well, sustained tobacco use, it is not something that I could possibly, from a chemical point of view, comment on. But just because these products are actually developed as alternatives to smoking, there is -- just logistically, of course, there is a possibility of sustained tobacco use, plus levels of unprotonated nicotine in some products are as high as in conventional products that have been shown to induce and sustain addiction. So this concern is justified.

Talking about addiction and graduation in new users, I showed that flexibility of the brand, I believe it does support chemistry; from a chemical point of view, it does support this concern. But again, this is just an isolated factor, chemical

composition of product itself, and there is a lot of research that needs to be done to look at the whole interaction between multiple factors to answer these questions.

There is a whole concept of relativity. When we talk about these risks, are we comparing it to higher, more toxic alternatives like smoking or conventional products, or we compare it to no tobacco use at all? Or when we talk about users themselves, is it switching from highly toxic products to these ones, or is it new users who wouldn't be exposed to any kind of tobacco carcinogen starting using these products? So it's very complex, and we have to keep it in mind.

When it comes to, also, health risks, are we talking about public scale, actually, or are we talking about individuals? Compared to smoking, there was a study showing a kind of review. We all know about this review that showed that use of low nitrosamine products leads to about 5 to 10 percent risk of mortality, overall general mortality risk, of cigarette smoking.

It is a great, great reduction in risk. However, if you think about those individuals who do actually get sick, does it make their well-being less meaningful because these are just 10, not 100 people.

So with that, I'm done at this point.

DR. SAMET: Thank you. I'm going to suggest that we move to the next presentation, which also covers somewhat similar territory, and then perhaps discuss the two together.

So next we'll hear from Dr. Watson from the CDC.

Presentation – Clifford Watson

DR. WATSON: Good morning. Can everyone hear me okay? My name is Cliff Watson. I'm the laboratory chief of the tobacco laboratory at the Centers for Disease Control and Prevention. We're in the National Center for Environmental Health emergency response to air toxicants branch.

As many others have read this morning, there's a disclaimer on my first slide here that the findings and conclusions of this presentation have not been formally disseminated by the Centers for

Disease Control and Prevention and should not be construed to represent any agency determination or policy. So pretty much I'm on my own here.

So we undertook this project of looking at dissolvable products at the request of the Center for Tobacco Products. I believe this was prompted by the appearance of several new dissolvable products on the market that appeared in 2009, including the Camel products and the Marlboro and Skoal sticks. Also, we included in our analysis the products that had been on the market since about 2001 and 2003, which are the Stonewall and Ariva products.

Our main focus was looking at qualitative analysis, although we did include some quantitative analysis of the data. Unfortunately, Dr. Stepanov and I did not talk before this meeting, and so there's a good deal of overlap here. So I will go through those, but I won't spend a whole lot of time on the areas that she's already covered since we pretty much mimic each other.

These are the products. I think everybody knows the products now. I don't really need to cover

these. These are the corrected slides in your handouts; there are a few typos. For instance, I had, for the R.J. Reynolds products, these appeared in 2005, which is obviously wrong. So thank you for loading up the new slides.

So I'm going to briefly skim over the quantitative analysis. These have pretty much just been covered in the previous talk. A very similar list of compounds -- sorry, not compounds -- products we looked at, different types.

We report in this table the weight, the measured pH, and in this particular slide, the nicotine on a per-gram basis of product as well as on a per-piece basis. Obviously, that way you can compare differences based on a single dose from a particular tablet or product or stick, as well as a general comparison on a per-gram of tobacco basis, tobacco weight.

We did do TSNA analysis as well. Our numbers are in good agreement with what was shown in the previous talk. Our focus here really wasn't so much on the individual products or product categories, but

looking at dissolvable products as a new sub-class of products, which may or may not be, based on the discussion today, a good approach.

So really what we're trying to focus on is what are the ranges of deliveries. And that's what we have in the bottom of the table here, is the average and then minimum and maximum deliveries. Again, Dr. Stepanov did a very good job of discussing this, and I don't think we need to dwell on these tables very much.

I did include in the presentation handout some data on metals. I took them out of this presentation just for convenience for time. We did analyze a number of metals quantitatively. The levels are reported in the same way we reported the TSNAs and nicotine, on both a per-gram and a per-stick basis. If you look at the metals data on a per-gram basis, these are typical to what range of values you see in other commercial smokeless products.

For the qualitative screen, which is really the focus of the talk today, is trying to just see

how different or similar are these new products, or new class of products -- they're not really new since some of them have been on the market for a while. But how do they compare? Are they more like conventional smokeless tobacco products, or is this really a new subcategory? And that's the reasoning we had when we were looking at these, trying to make these determinations.

Really, this was sort of a screening exercise. What's out there? What's included in these products? How do they differ, if any, from conventional products?

Our approach was to take approximately half a gram of material. It was weighed so we knew exactly the amount. This was dissolved in a -- or solvent extracted. And we use a variety of different types of solvents to try to get the maximum number of compounds we could extract out, looking at both aqueous extracts using added acid and base as well as a variety of organics.

What we found was the polar organic solvents were the most efficient extracting the greatest

number of compounds. So things like acetonitrile or MTBE turned out to be a very good solvent for this type of work. Of course, we always added internal standard to get some relative concentration effects so we could tell where we were. Samples were worked up and basically extracted.

Rotated at 60 minutes. The sample extracts were then filtered to remove any suspended particles and solids, and then concentrated. And the concentrated extracts in most cases were analyzed by simple gas chromatography with mass spectrometry detection. There are a few exceptions to that, and I'll point those out as we go along.

I don't really think we need to get down into the weeds about how we actually did the analysis. If anyone's interested, I'd be happy to discuss this with you. This is pretty much a standard analytical instrumentation, pretty much a standard workup in terms of the methods; nothing strange or exotic here. But again, if anyone has any questions, I'm more than happy to talk about the analytical aspects of the methods.

There are some limitations of this approach. Really, we're limited to looking at compounds that are volatile or semi-volatile. These are things that basically, when you put them in the inlet liner of a GC, you have a sufficient volatility and stability that they can make it through the -- converted into the gas phase, and then clicked on the column and then separated through the gas chromatography column. We did a couple different types of columns to try to achieve the optimal separations as well as playing around with some of the scan times to really try to pull some of these compounds apart.

We focused on looking at full scan data rather than looking at SIM data. And for those of you that know the lingo, basically this just gives you the easier way to search through and look for unknowns. The alternative detection method would be using selected ion monitoring, and typically you would do that if you're looking for a compound that you knew what the identity was ahead of time, and basically you wanted to get to a more accurate or more sensitive detection.

We are again limited to non-volatile chemicals that are thermally labile -- sorry, non-volatile chemicals or chemicals that are thermally labile are not very amenable to this approach. And so there is potentially some discrimination against things that are high in molecular weight or aren't stable at a high temperature.

Using the GC/MS approach, really we are limiting ourselves a little bit, and we're not looking at all of these so-called potentially harmful constituents. For example, things like heavy metals, the heterocyclic aromatic amines, aromatic amines, generally aren't amenable to this type of approach.

So for preliminary qualitative identification of the compounds that we analyzed, we were basically using one of the following approaches, a standard mass spectral library search; so where you have an isolated compound in the GC/MS and you compare that to a reference spectrum generally using the NIST library for identification.

We also did some work -- we had some questions about what the identities were. We were

fairly confident on the assessment of the peak, but went back and did some high-resolution mass spec work to confirm the identity of some peaks. And then for some compounds, we still had some questions. And then you can obviously inject a known compound. You can measure its retention time and see if it matches exactly to the compound you're interested in for more definitive assignments.

So this is a typical chromatogram of the type of -- this is indicative of the type of information that one can pull from this technique. Let me back up just a little bit here. For those of you that don't do GC/MS for a living, let me just explain what's going on here. And please, those of you that do, just indulge me for a second.

So on the X axis, we have time. So what the GC does is basically it separates each one of the compounds, or tries to, as a function of time as it comes to the columns. The column is a fancy sorting mechanism to sort out the chemicals, introduce a complex mixture. And it's trying to sort those out into their individual constituents. And then the Y

axis here is the relative magnitude. It basically tells you roughly how much there is of each one, which then you can go back and you can collaborate to get exact numbers.

So in theory, each one of these peaks corresponds to a different chemical. Now, there could be cases where things overlap a little bit, and one peak may not be fully resolved, so you may have more than one compound represented by a single peak.

However, we can go through using our recognition software and analyze all the major peaks here. And we can assign -- most of the major peaks we have assigned here. There are quite a few down here in the graphs you'll see that don't have assignments, and that just means that basically we weren't confident enough of our measurement, based on our library searching capabilities, to identify all these peaks. So I'll show you a table of compounds in a minute. But just keep in the back of your mind they're only identifying basically a subset of all the compounds that are present. Now one thing, there are techniques to go back and identify all these

little guys here, if you're interested in it. It's just more time-consuming.

Pay particular attention to peak number 6. This is an example here of our high-resolution capabilities. We weren't sure of the tentative identity of this. The libraries came up and suggested a couple of different possible hits that had equal chances of being correct.

What we did then is we took that compound and we analyzed it using a high-resolution sector mass spectrometer to get to the high-resolution, basically exact mass of each one of the mass spectral peaks. And based on this information, we were able to basically assign the identity of this peak, which is this horrible name here, N,N-dimethyl-7-undecenamide.

But just so the utility of -- the simple GC/MS approach gives you quite a bit of qualitative information, but in many cases, you need additional complexity to identify some of these harder-to-identify compounds.

So this is a list of preliminary identified compounds. Most of the ones on this particular table

are flavor-related or we believe related to the addition of flavors to the compounds. And this is a summary list of all the compounds. It's not sorted by product in this particular example. This table goes on.

We've tried to break these up into different functional groups. These range from things like carboxylic acids, things that we know are common to all tobacco products. And as everyone knows here, tobacco is a very complicated matrix. There are a lot of compounds in there. Of course, these dissolvable products are made from tobacco, and so we will expect to see many of the -- or all of the tobacco-related compounds.

Fatty acids, fatty alcohols, amides, humectants, some of the polymer residue, some of these other fatty acid esters, these are probably things related to the binder, the things that hold these things together or hold them glued to the tobacco stick, although that's just conjecture on my part.

So the simple 1D GC/MS approach gives us a

wealth of data. But as you can see, there are many, many peaks in that chromatogram that I showed you in that example where we didn't identify the peaks. And so what we wanted to do is apply more powerful analytical techniques to try to pull these apart so we could assign and identify more of the compounds present in these products. And we did this using a technique called two-dimensional gas chromatography with time-of-flight mass detection.

Again, for many of you, you probably don't care about the details of how analysis works. I have them listed here. If anyone's interested, I'd be happy to talk to you about this experiment. This is all pretty much standard for this type of analysis.

I don't know if you guys can see that. That's a little dark. My apology for the darkness of this slide.

Let me spend just a little bit of time explaining how this display works. I wish you could see it a little better here. But basically, instead of being a one-dimensional representation where you had a single line where each peak corresponded to an

individual chemical, this is a two-dimensional chromatogram. So basically, if you compressed everything down onto this axis here, this would be your one-dimensional representation. And what the two-dimensional does is basically it tries to -- when you have a complex mixture and you have overlapping compounds in each one of these peaks, it tries to separate them into this second domain.

So basically, it's just a way of pulling things apart by using different chemical properties to try to separate as many of these components as you possibly can so you can get a clean hit, which gives you better identification of the individual compounds.

So this gives you quite a bit more data than you do from the typical 1D experiment. And again, these are all tentative identifications, mainly based on library searching. This particular example is for the Camel orb. If you take the data from all the compounds where you've identified the peaks -- the slides obviously -- the tables are just too big -- and again we see tobacco compounds, what you

expect to see from things that contain tobacco.

We see many other common classes that we've seen before that we've already talked about. We're starting to see some new compounds that we really hadn't been able to resolve in the 1D case, some of the phenols and some of the chlorinated products, as well as some of the furans. And we're getting better detection on some of the phthalates and other compounds.

So the 2D approach has a lot of utility in terms of being able to screen tobacco products -- well, to screen any type of product, for that matter, and if you're trying to look at what's present in these very complex mixtures.

This is just continued from the previous slide. And you can see there's quite a bit of different chemicals in here, some of them related to -- like vanillin -- flavors. Some are probably just coming from the tobacco itself. But these are ones that are typically seen in these type of tobacco products.

So a couple points I wanted to talk about

today in summary is that the GC/MS provides quite a bit of information. You can get even more information from the GC/MS MS. I think in that example we showed for the Camel -- I think it was fresh orb -- in the GC/MS, we were able to -- you see uniquely about 300 peaks. We were able to tentatively identify about 32 of those where we felt confident in our identification. Many of the other compounds we were able to identify, but not with a great certainty. And so we need to follow those up with either the high-resolution mass analysis or run reference standards where we knew what the compounds were to check retention times to confirm their identity. So we saw about 300 peaks and were able to identify with good specificity about 32.

The same sample, by the GC approach, we were able to see about 1700 unique peaks and tentatively identify about 160 of those using our library searching approach.

So these approaches provide very good qualitative information. One could go back now after you've identified peaks or you've identified

components that you're particularly interested in and you could basically build calibration curves and, in a QA/QC environment, you could quantify the levels of these constituents in the products, the one limitation being is many of these compounds are only amenable to analysis by the GC approach. They're volatile or semi-volatile constituents.

Things like the metals are generally analyzed by an approach called ICP/MS, which is a standard method for metals analysis for many different types of applications, not just tobacco. For the constituents like the tobacco-specific nitrosamines, the heterocyclic aromatic amines, many of the heavier non-volatile components, the method of choice for those analyses is using an approach called LC/MS, liquid chromatography instead of gas chromatography.

The down side of those for this type of survey work is that generally there are no good library databases that you can use to identify unknown compounds. They're great techniques when you know what you're looking for and you want to quantify their levels, but they're not great at screening.

And that's why we stuck with the GC approaches for this talk today.

Dissolvable products, like other tobacco products, are chemically complex. We know that tobacco is a very complex matrix, and with the various flavor additives used in these as well as the binders and the things to hold the tobacco products, little pellets, together or to the stick, we're seeing some new compounds that we haven't seen before. So this is a new area of research.

Again -- I mentioned this already -- this approach is not really particularly amenable to thermally labile compounds. So the chemicals I've shown you in these tables are by no means an exhaustive list, and this is basically just a smattering of the compounds that were amenable by this particular approach.

So the conclusion is -- the conclusion of all sort of scientific talks, right? -- more work is needed.

[Laughter.]

DR. WATSON: But work would be required to

confirm the tentative identification of these. And if any were identified as being of particular concern, then we would need to go back and build quantitative methods to actual measure their quantitative levels. And so we'd have good confidence, not only in the identity of the compounds but also in their levels in these different products.

Thank you for your attention.

DR. SAMET: Thank you. And thank you to both presenters. I think we might discuss these now. Don't worry, there's not going to be a chemistry test.

[Laughter.]

Committee Discussion

DR. SAMET: Actually, let me lead off because -- a question to both of you. We didn't see any information on within-product variation in these measurements. Did you test enough product within any of the particular products to get a feel for how much range there is within product? Please.

DR. STEPANOV: The question is, within product, let's say different samples of the same

brand, the same flavor, for example.

DR. SAMET: For example, yes.

DR. STEPANOV: Yes. So we had four dissolvables. Except for Ariva and Stonewall, our samples generally came from three different locations, not necessarily in different states -- it could be the same state -- just three different stores. So we had three samples. And numbers that they showed were averages of analysis for these three samples. And they pretty much agree, very closely, for dissolvables.

DR. SAMET: And you purchased your products in stores? Is that what you said? Or where did you get the product?

DR. STEPANOV: Right. It's part of an ongoing project that is called New Product Watch, in collaboration with Lois Biener. And so the products are purchased and sent to us for analysis.

DR. SAMET: And your products came from?

DR. WATSON: Our products came from FDA. We really weren't focusing on individual product variation. I think almost all the products were from

the same lot. So I don't have good data on this, yet I hate to speculate, but the data were very consistent.

I'm not sure if our products overlap with Dr. Stepanov's products. But looking at the slides this morning as we were sitting there together, there's good agreement between the two different methods. And so there seems to be a fairly good amount of consistency within the products.

But I think if one really wanted to ask this question, you'd need to look at a range of different lots and see is there lot-to-lot stability.

DR. SAMET: But your results actually I think did differ on pH. With hers, I think the Ariva values were all around 6.8, 6.9, and I think for you they were about 7.5. There were some differences that I'm not sure I fully grasp, but might be something for you to look at.

Okay. That was just something I wanted to clarify.

Let's see. Questions from the committee. I'll start it this way. Fred?

DR. PAMPEL: A bit of a naive question. But what's the amount of the NNN and NNK in a cigarette compared to the smokeless tobacco, and is there a one-to-one correspondence between cancer risk so that if cigarettes have five times as much of the cancer-causing chemicals, the risk of cancer is five times as great?

DR. STEPANOV: Well, this is exactly that relativity concept that I kind of mentioned at the end. It's very difficult to compare the same constituents in cigarette smoke versus smokeless tobacco because the route of administration is completely different. The place of absorption is different.

So you can't really compare one-to-one exactly the same amount that is present in smokeless product versus cigarette smoke, and compare actual potential with fact. So it's a very complicated question.

I don't know if you have a comment, Cliff.

DR. WATSON: We need to talk to some of the toxicologists, I think. That's outside my area of

expertise.

There were some differences in the nitrosamine levels, particularly with the Star products being lower. But how that translates into potential health consequences, I don't know. I can't address that.

DR. STEPANOV: One of the ways to address it is to look at biomarkers of exposure, which would be a more direct way to estimate actual intake because with cigarettes, you have levels in tobacco that has to be transferred in the smoke and then partially absorbed; while, let's say, if you talk about dissolvables, it's pretty much what you measure that in theory should equal the intake because everything goes in the body. So biomarker approach would address this question.

DR. SAMET: Dorothy?

DR. HATSUKAMI: I have a question, Irina. Could you let us know what the levels of NNN and NNK are in some of the Swedish products as well as maybe the unprotonated nicotine? I know you might have that data.

DR. STEPANOV: I have probably too much of the data to remember it right now. But overall, Swedish products are known to be low, relatively low, in TSNA. I think that some of these dissolvable products are even lower than what is found in Swedish snus. Some have levels comparable to U.S. conventional products.

As it comes for nicotine, I don't think I remember at this point the exact amount of nicotine in Swedish snus.

DR. SAMET: Let's keep going. Bob, did you have a question?

DR. BALSTER: Yes. I have two questions, one really quick. There's been conjecture that acetaldehyde has a pharmacological role. I don't see acetaldehyde on your list. Is it something that you didn't find, or is one of the things you just didn't list?

Is acetaldehyde found in these products?

DR. WATSON: I don't remember specifically if we identified that. There were a lot of compounds. I'd say, we're really only seeing the tip of the

iceberg. There are a lot of ones that we couldn't resolve, or we couldn't have any confidence in the measurement that we were willing to state that, yes, we're fairly confident we're seeing that compound.

That did pop up in a lot of searches. I think it's likely present. But I don't have any definitive data saying that it's there or what levels it would be at.

DR. BALSTER: The other question is purely hypothetical, and I hasten to say, in asking it, I'm not implying that industry is doing this or has any intentions of doing this. But would the methods that you're using be able to identify if, for example, a genetically modified tobacco was used that introduced a gene, say, for example, to add a novel alkaloid that could alter the pharmacology of nicotine in some way; or, for that matter, if a novel alkaloid was introduced into the product someplace in production?

Would you be able to identify a novel alkaloid of that type pretty readily?

DR. WATSON: It would be difficult. Basically, you would be looking for a needle in a

haystack. It's a very complex chemical mixture. If you had some evidence or some hypothesis that guided your direction, you might be able to fish those sorts of things out. But just in routine screens, unless it was just at huge levels or just happened to be cleanly isolated from everything around it, it would be hard to pick out in just routine battery of tests.

DR. SAMET: Let's keep going. Who else? Continuing around. Neal?

DR. BENOWITZ: Irina, do you have any data on the effects of storage? Because I know that Swedish snus is supposed to be kept refrigerated, and they do a lot of things to prevent the generation of nitrosamines over time with storage.

Is there any generation of nitrosamines if dissolvable products sit around or are put in hot environments or things like that?

DR. STEPANOV: Well, we didn't do these kinds of experiments. But yes, it is a known fact that additional amounts of nitrosamines can be formed in smokeless tobacco products that are being stored at elevated temperature and moisture content.

I think that in case -- it depends on how product is produced as well. So if you have pasteurization involved, I would think it would kill most of the bacteria that are involved in conversion of nitrate to nitrite and generation of additional amounts of TSNA during storage.

So I think that, again in theory, the possibility of additional formation of TSNA in these kind of products would be lower than in conventional products, but we didn't do, actually, any kind of analysis to test this hypothesis. One thing that we do, we do refrigerate. We keep products to prevent artifact formation for our analysis.

DR. BENOWITZ: Have you done studies looking at urine NNAL with various products? Your group?

DR. STEPANOV: My group, no. But I know that there is work that is -- I believe there is work that is being done.

I think, Dorothy, could you comment?

DR. HATSUKAMI: No. We're not doing the dissolvables.

DR. BENOWITZ: And then another question for

you both, but it may be for the tobacco manufacturers later on. I'm just curious to know, what's the source of the differences in nitrosamine levels in different products? Is this from the different tobacco? Is it from the manufacturing process? Why are there such big differences? And the same for pH. Why are they different?

DR. STEPANOV: Well, tobacco-specific nitrosamines are formed during tobacco processing. So there are just trace levels that can be detected in green tobacco leaves. And the levels depend on a really complex set of factors, starting with the type of tobacco, what kind of tobacco is used, soil where it was grown, whether or not there is elevated levels of nitrates that are sources of nitrosating agents that eventually interact with tobacco alkaloids and lead to the formation of TSNA; the results of processing approaches that greatly influence TSNA formation, fire-curing versus flue-curing of tobacco.

So I guess there are too many factors, which explains wide variation of TSNA levels in different products.

DR. SAMET: I think, actually, I'm going to move the discussion along. We're getting a little bit too far behind.

So why don't we keep going with further questions on the presentations.

Sandrine?

DR. PIRARD: A question to Dr. Watson. Just as a reference, if you were to for example, use those same techniques and analyze like Listerine strip, or more complicated or kind of similar, what would those products appear to be as compared to that?

DR. WATSON: Of course, we haven't done that work. But something like a standard Listerine strip obviously doesn't -- presumably, it doesn't contain tobacco. So my guess would be it would be a much less chemically complex matrix, and so you'd be able to get a much cleaner picture and be able to identify more of the different peaks. But again, speculation on my part.

DR. SAMET: Yes, Tim?

DR. MCAFEE: I have two quick questions. The first is, essentially, I guess I would just

echo -- this is kind of a request that I think Dorothy was alluding to. I think it would be helpful to see how the class, to the extent there is a class, of dissolvables compares to other smokeless products in terms of these characteristics. Because it's hard to really get a sense of, is this horrible, is this better? So I think at some point that would be of assistance.

The other, I really had a question, Cliff, for you. You're creating this very large list of chemical compounds. And essentially, what are you thinking of for next steps for making sense of this? How do we determine where to go with this much information in terms of determining particular chemicals that may be of particular use and need to have further exploration, or what are you thinking?

DR. WATSON: Well, this was work that was done at the request of the Center for Tobacco Products. And really, we're just trying to get a handle on -- you can't really call this a new class of products because the Star Scientific product has been around for a decade or so. But with

introduction of the new products, it does appear there's emergence of a new presumably sub-class of smokeless tobacco products.

So really we're just trying to get a handle on are these similar or how different are they from other smokeless? Where the discussion was going this morning, can we use the older data on smokeless tobacco products to help us guide any thoughts or processes about the emergence of these new -- not emergence of these new, but these new products?

We are collecting a large amount of data on these. We're doing internal reviews, trying to decide -- comparing them to a list of the HPHCs as well as other databases where we think there might be some chemicals of concern, and working with other partners trying to decide what are our next steps.

Right now, we're basically just trying to build a database for comparison between these products and other existing products to see, really, what's the nature of the overlap; are they similar or are they different?

Further work I think is up for debate. I

think there's a lot of very interesting applications moving forward, and we are open for input.

DR. SAMET: But I would say, I think, in answer to Tim's question, which is what I had on my mind, this is a common problem dealing with high-density data, and resolving it down to what might be signatures, and seeing how those signatures differ across products. I think that's a very common analytical problem these days for which there are many different sorts of clustering approaches.

Why don't we move on. Mirjana?

DR. DJORDJEVIC: I would just like to follow up on Neal's question about huge variability in nitrosamines among different products. As you can see, Star products are very low in nitrosamines, and then Marlboro's are very high, and Skoal.

It would be helpful also to determine whether the type of tobacco is the underlying factor. If you would break NNN from NNK when you would present your results because, like for instance, flue-cured or burley tobacco, they have a different pattern in formation of these two nitrosamines.

So if you would do so, then you probably would find out that Skoal and Marlboro are probably made from different type tobacco, which doesn't really control very well for nitrosamine formation. So that's like one issue. And you also see much higher nicotine content in those two brands. So that will give you idea what type tobacco is used.

Another question I have for Cliff. In your second slide when you gave the outline of your presentation, you said you were measuring five tobacco-specific nitrosamines. I assumed that you also meant NNAL, but then you later didn't present that.

So do you find NNAL in this type of product?

DR. WATSON: We did analyze for NNAL. It was very low, and in many cases, it was below the limit of quantification. And just to make the slides easier to read, I took it off because I didn't think it was that informative.

DR. DJORDJEVIC: No. I understand that. But that could be issue later when we work on biomarkers, to know whether biomarkers come from exposure to NNK

or they just transfer from tobacco.

Also, just one more question for you. When you worked on volatiles, did you measure any quantities of volatile nitrosamines, like nitrosodimethylamine or --

DR. WATSON: We did not look for those specifically, and I don't think we saw those in any of the screening hits that we got. Presumably they could be there, but they're probably buried beneath other peaks.

DR. SAMET: Okay. I'm going to take the first question as a comment and move on to Dan.

DR. HECK: Just a quick follow-up to some of these questions that have been floated. I think it's fair to say, for the snus and the dissolvable-type products, which both tend to use similar types of tobacco, yes, the type of tobacco is one determinant of the nitrosamine level, for instance. But I think probably more important is the drying and curing process. That's markedly different for these recent product introductions. I think that's where the big difference in the nitrosamines primarily comes about.

There was some discussion about the nitrosamine levels relative to cigarettes. We didn't quite get clarity there, but I think we can find that in the literature. And that led to a question about biomarker studies. I don't have at hand -- my memory -- I do suspect, in fact I'm quite sure, there are biomarker studies available of some of these new products.

The only one I'm thinking from memory, recalling from memory right now was presented by Altria at the LSRO, a reduced risk process some years ago. And it was an early version of the product of the day. It may have been a snus or early dissolvable; I'm not recalling.

But I was recalling that I was struck by the NNAL levels, that were reported for stable switchers to the snus product were indistinguishable, statistically, from nonsmokers. And the smokers' levels, of course, were quite elevated and easily detected. So I thought that was a pretty remarkable finding.

DR. SAMET: Thank you.

John?

DR. LAUTERBACH: Dr. Watson, if pH is defined from pure aqueous solutions, how then do you compare or justify comparison of pHs of aqueous extracts where the aqueous extracts are quite different in composition? And then how do you then justify the extension to an unprotonated nicotine value?

DR. WATSON: There are standard methods published for looking at pH in smokeless tobacco products. Basically, you take a fixed amount of the product, you grind it up in sort of powder form, you dissolve or suspend that into a fixed volume of water, and then you measure the pH probe.

So what you're measuring then is the resultant pH of that solution. And so one would expect that relative difference between the different measurements would give you some indication of the relative pH of the products.

DR. LAUTERBACH: But that doesn't fit within the embedded use of the Henderson-Hasselbalch equation.

DR. WATSON: Well, that's been the generally

accepted way this has been presented in the scientific literature, and basically, we follow the same principles.

DR. SAMET: Patricia?

DR. HENDERSON: Dr. Stepanov, I had a question about the role of menthol and the graduation steps that you were talking about and whether that's true for dissolvables and smokeless tobacco.

DR. STEPANOV: Well, I don't think I can give a comment on this because addiction is not actually area of my expertise. So I don't know if Cliff can comment on this.

DR. WATSON: We did see menthol in these products. Unfortunately, it wasn't one of the compounds we were quantitating, and so I can't tell you what the relative levels are in the different products.

DR. SAMET: Let me go to the phone and see if Mark or Arnold have questions, comments.

DR. CLANTON: Nothing here.

DR. SAMET: We can hear you.

DR. BENOWITZ: That was a "Nothing here."

DR. SAMET: Let's see. Does anybody have anything there?

MR. HAMM: No comments for me.

DR. SAMET: No comments. All right.

Let me go back. So the last two very quick comments, Dorothy and Tim.

DR. HATSUKAMI: I just want to make a correction. Neal, I forgot we did do a study with Ariva. Sorry about that. And what we found is that among those who were given Ariva, their NNAL levels were really quite low and they were indistinguishable from the medicinal nicotine product, the nicotine lozenge that we were looking at. On average, the people had used about 7 to 8 Arivas per day, and that's the levels that we attained.

DR. SAMET: Tim, your 10 seconds?

DR. MCAFEE: A quick in vivo versus in vitro question. pH in a product that's being dissolved in the mouth, how convinced are we that it matters what the pH of the dry product is as opposed to what happens once it's dissolved in saliva, but which is, I think, a buffered solution?

DR. WATSON: That's a very good question.

DR. STEPANOV: I think there was a reference that shows that buffering capacity of smokeless tobacco, not dissolvables but like moist snuff, is higher than buffering capacity of saliva. I've seen the reference. It's not something that is a result of our own studies.

DR. SAMET: Tom? Last question.

DR. EISSENBERG: Yes. Just on the subject of biomarkers, we also did a study where smokeless tobacco users were exposed to five days of Stonewall or five days of general snus. We saw a significant decrease in urine NNAL levels with Stonewall but not with the general snus.

DR. SAMET: Good. Thank you very much to the two presenters. Obviously, there's a great deal of interest in your work. Thank you.

So we're going to move on to Sarah Evans, who will talk about the topography of dissolvable tobacco products.

Presentation – Sarah Evans

DR. EVANS: In the interest of time, you

heard the disclaimer from FDA this morning, so I'm going to skip over that.

DR. SAMET: If we could eliminate all disclaimers, we'd have saved 30 minutes across the three days.

[Laughter.]

DR. EVANS: It makes the lawyers happy.

An overview of my talk today, I'll be talking about general product information. I'll give you a little background, and I will speak about the topography of smokeless tobacco products and topography of dissolvable tobacco products.

This is a picture of some of the currently available dissolvable tobacco products. I think you've seen these before, maybe some new ones. We've got Camel's orbs, strips, and sticks; Marlboro and Skoal sticks; Stonewall, Ariva, and NicoSpan, which is a strip. This is also a picture of a recently available product from R.J. Reynolds. It's the Viceroy Flex. It's dissolvable tobacco as well.

The nicotine levels by product, we heard today that they do vary, but I've put the levels up

again. FDA reports these in milligrams, so Ariva is 1.5 milligrams, Stonewall is 4. You can see that the Camel products vary starting from .6 up to 3 milligrams, and NicoSpan is 1 milligram. For the Viceroy Flex, the Skoal stick, and the Marlboro stick, the nicotine levels are not publicly available.

So what is topography? Topography assesses human tobacco consumption behavior. So a smokeless tobacco, topography measures include self-reported measures of tobacco use such as tins used per week, total dips per day, total daily dip duration, and the total daily dipping time, which is the time from the first dip of the morning till the last dip of the day. Dissolvable tobacco product topography measures could include similar measures of quantity, frequency, and duration of use.

There currently exists no standardized method for measuring the topography of oral tobacco product use, and there is very limited information available on the topography of dissolvable tobacco products. Well, can we learn, then, from the experiences of

other tobacco products to help us understand what topography might be expected from dissolvable products?

I'm quoting now from a study from Lemmonds, et al. It's a topography of smokeless tobacco study. It's publicly available. "In this study, male smokeless tobacco users aged 21 through 65 were recruited for a study that compared nicotine replacement products and new tobacco products. Participants had used at least one tin of smokeless tobacco per week for a minimum of 1 year, and the topography data came from a two-week baseline of ad lib use of smokeless tobacco."

So 54 participants -- they were around age 32 -- recorded the time each dip was placed in and removed from the mouth.

"Outcome measures from the study included nicotine, cotinine, total nicotine and total cotinine, NNK, and NNAL. The results suggest that frequency and duration measures of smokeless tobacco use, particularly total dip duration, are significantly correlated with total cotinine, total

nicotine, and total NNAL."

This is a table I really just want to illustrate. These are the measures of topography, and this is how they can be useful. So here it shows dips per day, tins per week, average total daily dip duration. Again, this just illustrates what topography measures are.

In addition, I'd like to orientate you to this graph. On the bottom here, we have total NNA exposure and also total dip duration. And as you can see, as total NNAL levels increase; they increase as total daily dip duration increases.

So now I'll move on to the topography of dissolvable tobacco products. TPSAC specifically requested information on the variability of how dissolvable tobacco products are used. And I will be referencing three studies today, and the data from these studies shows the topography measures from that study.

These studies are provided in your background materials and are all publicly available. I'd like to emphasis that the conclusions drawn are the

author's conclusions and not FDA's conclusions.

The first study I'll be referencing -- I should say that with the three studies, there are three slides each, and they're all formatted the same to show you what product was used, what was the objective of the study, and who were the participants.

So this was a clinical laboratory study. This is a 2008 study by Gray et al. The type of dissolvable tobacco used was Stonewall, and it was five days of ad lib use. The participants used only Stonewall; there was no concurring use of other tobacco products. And how they used the product was per package instructions, meaning participants were asked to place the product in their mouth and allow it to dissolve, which takes around 15 minutes, and there was no chewing or swallowing of the product.

There were 19 participants. No women. Around 24 years of age. All had used less than five smoked tobacco products during the last six months, but reported current use of smokeless tobacco on a daily basis for the last 12 months.

The objectives of this study were to adapt models used to examine cigarette-like potential reduced exposure products for smokers for use in the evaluation of toxicant exposure and abstinence symptom suppression for smokeless tobacco users.

The author concluded that the amount of dissolvable tobacco product used, expressed as a percentage of product provided, was significantly higher for Stonewall versus snus and own brand, but Stonewall had lower CO, cotinine, and NNAL levels versus own brand smokeless tobacco.

The second study I'm referencing today is by Blank et al., also a clinical laboratory study. The study used Ariva. It was five days of ad lib use; no use of other tobacco products; also used per package instructions.

This had 21 participants, including 6 women. Participants were about 33 years old, had used about a pack a day for at least one year of cigarettes, and the objective of this study was to measure toxicant exposure, abstinence symptom suppression in smokers.

The author concluded in this study that

during five-day conditions, the mean number of Ariva consumed, collapsed across the day factor, was 12.3 versus 21.9 cigarettes and 11.7 snus. The average scores for "Are the tobacco products you are using this week pleasant?" were significantly lower for Ariva versus cigarette, but higher for Ariva versus snus, and Ariva had lower CO and cotinine but not NNAL levels versus cigarettes, but similar CO, cotinine, and NNAL levels versus snus.

The last study I'll be referencing today is by Carpenter and Gray. This is a clinical trial where participants used Stonewall for 14 days ad lib use, and this product was used concurrently with cigarettes. Stonewall was used per package instructions, similar with the other studies.

Participants. There were 19 participants, including 7 women, about 42 years of age. They had used at least 10 cigarettes for at least a year, and they were regular smokers.

The objective of this study was to measure influence of short-term smokeless tobacco use on smoking behavior and cessation in smokers who were

unmotivated to quit. I should emphasize the participants were told of the study purpose, which was to measure changes in smoking behavior while using the new tobacco product.

The author concluded that dissolvable tobacco use was an average of 7.7 pieces during week 1 and 7.5 pieces during week 2. Fifty percent of participants used dissolvable tobacco more than a few times or frequently to cut down on their cigarettes smoked. Thirty-nine percent used dissolvable tobacco products to cope or avoid smoking restrictions, and use was more predominately to use to avoid smoking restrictions at work.

So I'd like to tell you now about the study limitations. These studies were not designed specifically to examine topography, and most studies examine users of combustible tobacco products, not users of dissolvable tobacco products. These studies did not assess compliance with dissolvable tobacco products or uncontrolled use of other products throughout the duration of the study time. And these studies were of a short, one- to two-week duration,

so perhaps not enough time to establish consistent use behavior of a product.

In summary, there currently exists no standardized method for measuring the topography of oral tobacco product use, and more clinical research is needed, as well as standardized clinical evaluation processes to evaluate the topography of dissolvable tobacco products.

DR. SAMET: Great. Thank you. You helped us catch up. I'm not sure we got what you said, but you helped us catch up.

[Laughter.]

DR. EVANS: Do you want to do questions now or questions later?

Committee Discussion

DR. SAMET: Actually, I think what we should do is we should have questions about this and then go on to the next presentation, which is somewhat different.

Actually, I was going to ask on your slide where you say there exists no standardized method for measuring the topography, and I guess I was going to

in part turn to Tim and just ask about at least questionnaire approaches that have been developed.

I'm thinking about the GATS, the Global Adult Tobacco Survey, where there's been some effort to develop standardized questions. I know in India there was a grappling with very different patterns of oral tobacco use.

So from the side of CDC data collection and surveillance for oral tobacco products, where do you feel you are versus this statement, there's no standardized method? That is, I'm sure, true, but there have been standardized approaches that have been taken.

DR. MCAFEE: Well, I'd say the short story is that we're in a transition zone; whereas before we were really just treating it as an entire total class, and now we're trying to move into more specificity in the different surveys that are being conducted across agencies.

But it's going to be hard certainly to go back retrospectively and ask meaningful questions about use. But we have been looking at and are

starting to report on patterns of use around things like dissolvables and other tobacco products like e-cigarettes that are beyond the scope of this particular meeting.

DR. SAMET: Yes, Neal?

DR. BENOWITZ: So just a follow-up to that, and maybe either Sarah or Tim would know.

Epidemiology data on use -- these are three experimental studies.

DR. SAMET: Right.

DR. BENOWITZ: But if we just look at the general population, how many of these products do people use per day, on average? Do you have a sense of that?

DR. EVANS: We don't have a sense of that, no. It's just an emerging area. But we would look forward to your discussion, actually, of what you'd like to see. These studies were not designed to look at topography, so I pulled the topography measures out. But it would help FDA to have the discussion of what measures you would be interested in looking at.

For example, these studies were done in

Virginia and South Carolina. Are there regional differences? Are there gender differences? If you could elucidate what you think would be helpful, that would help us.

DR. BENOWITZ: So from all the national surveys we have, we have no data on how many --

DR. EVANS: I know we have just put in questions from one survey. I know that we don't have -- FDA doesn't have the information, but we can gather it.

DR. MCAFEE: Yes. The next round of the National Adult Tobacco Survey will drill down.

DR. EVANS: Yes.

DR. MCAFEE: And the youth surveys will drill down with more specificity. I can try to get more information shortly about, literally, the specifics of which questions are asked. We can get that.

DR. SAMET: Bob?

DR. BALSTER: So one of the relatively important characteristics of these dissolvable tobacco products, there's a low nicotine exposure. It seems logical that people might attempt to

compensate for that by taking multiple products at the same time.

Were there any instances in these ad libitum clinical studies of people doing two pieces at a time, or are you aware of any other data on that sort of a use pattern?

DR. EVANS: They were not reported in these studies. But again, these are just three studies, and they were instructed to use these per the package instructions. So what they did on their own time, we don't know if they used four at a time. We don't know if they swallowed them. We don't have that information.

DR. SAMET: Ellen?

DR. PETERS: I realize you said that these were fairly short-term duration studies. But was there any indication, even with this kind of short-term duration, that people actually kept up with taking these products or actually started to discontinue use, even after a short time?

DR. EVANS: I think Dr. Eissenberg could answer some of those questions in terms of dropout.

I know that there was some issue with people not perhaps liking the product or issues with withdrawal suppression.

DR. EISSENBERG: Yes. I think that's a great question. And in the one with Ariva, Blank and Eissenberg -- I'm looking at it now -- these were smokers who were asked to abstain from all tobacco use. And we had 13 people who simply couldn't do that for the five days of the study.

Then in another case they were asked to use Ariva only, so the smokers were asked not to smoke but to use Ariva. Seven people couldn't complete it because of that requirement. And the same number, 7, couldn't complete the Camel snus conditions because they relapsed to cigarette use. And this is when we're asking them to and in fact paying them not to use cigarettes. So I think that's really important. And there are similar data for the smokeless. I just don't have it in front of me for the other study.

DR. PETERS: If I could just ask a follow-up also. Was there anything in those studies looking at people's perceptions of how healthy the products

were? So, for example, in the Blank, et al. study -- I believe it was that one -- so you knew that from the Blank et al. study that there were differences in how pleasant they were. Were there also differences in perceptions of how healthy they were, or some other attribute that might have been important?

DR. EVANS: As I recall, I think it's just general liking, was it pleasant; so subjective effects, not health perception.

DR. SAMET: David?

DR. ASHLEY: I got an answer, partial answer to your question, from the audience. Just to let you know, be aware, the PATH study that is beginning now will take -- it's going to take some years to collect the data. But that study will help us get some more information on exactly some of the topography measures of how these dissolvable tobacco products are being used.

DR. SAMET: Others? Let's see. Mark? Arnold?

DR. CLANTON: Nothing.

MR. HAMM: No comment from me.

DR. SAMET: Thanks.

So all right. Good.

Well, thank you, Sarah. And we're beginning to catch up a little bit so we can have lunch today.

[Laughter.]

DR. SAMET: Our next presentation, from Miranda Spitznagle on Indiana's experience with marketing of dissolvables. Thank you for coming.

Presentation – Miranda Spitznagle

MS. SPITZNAGLE: Good morning. I'm Miranda Spitznagle. I'm with the Tobacco Prevention and Cessation Commission of the Indiana State Department of Health. It's a pleasure to be with you here this morning.

I'm going to share -- Indiana has a somewhat unique history in the fact that we've been a test market for I think about five tobacco products being tested in our area since 2001. This ad is just a simple counter-marketing ad that our youth movement used to kind of illustrate that history, being a guinea pig for some of these products.

My comments today are going to be specifically on our experience with the Camel dissolvables that were test-marketed in Indianapolis. Indianapolis was chosen in early 2009 to be one of its test markets, and in my time I'm going to share a little bit about what we experienced with that, that marketing of the products in our state. This was a little bit of our community response to those as well.

First off, even as our state program was learning about these products coming to our area, our state poison control center issued this news release just highlighting the potential concerns of the product being on the market for consumers, parents, as well as pediatricians.

As you can tell and has been brought up before, the photos look like familiar items such as mints, breath strips, cinnamon sticks, and toothpicks. And so the concern is which is which, and it can be easily confused.

In February of 2009, we happened to be planning a youth empowerment event in our state. And

so we took that opportunity to ask some of our youth if they had seen some of these early marketing materials and some of the products in their communities.

So we did, again, just a very informal sort of focus group with these youth and asked them a couple of questions. The first question was if they had seen or heard of them early on in their community. And as you can read from the slide and some of the general comments, they were -- the youth generally noticed that -- they thought that most people wouldn't really recognize the products as tobacco, and commented that they looked like other items, as you saw in the photos earlier. And as you can tell by the last comment there, about something that could be easily concealed. And so, you know, a youth commenting that I'm just going to take these pellets -- and at the time, orbs was the first product on the market -- take them, put them in some sort of a mint can, and no one's going to know what I have.

The other question was a few comments about

what they thought about the marketing campaign in their community. And again, you can see here some of the general comments. Again, these are summarized general comments that we got from the youth, but overall felt like they were not really targeted to current tobacco users and something that adults wouldn't really catch on to.

So we, as part of our state tobacco control program, alerted our network of local coalitions around the state, asked them to let us know what they were seeing in the retail environment and their communities and let us know.

This slide summarizes some of the anecdotal comments that one of our local coalitions did see. You'll notice that they commented about the signage that was in the retail establishment, and they also commented on the interaction they had with the sales clerk in that retail outlet. And overall, the sales clerk was not knowledgeable about the product, didn't really know what they were.

When asked about the product and how they were used, there were misperceptions about them being

a diet pill, and people had been getting sick who had used them. And I will say from personal experience, in the outlets that I had visited as well and the retail environments not really being knowledgeable about what they were.

This is just an example, although fuzzy, but an example of the signage that was seen at the retail environment.

Among the reports that we did get throughout the state of Indiana from our local coalitions, this map provides a summary of the product reached by county of the two products that were out at this time. These were data as of April 2009. And you can see that a lot of these products extended further than the Indianapolis market, which is the central Indiana region of our state. And so a lot of these products were seen up to our northern border, which touches Michigan, as well as further into the southern part of our state.

Next I'm just going to give you some examples of some of the marketing tactics that we saw in our state, a lot of online presence with websites, plus

the use of social media and those types of marketing; retail store coupons. Many of us used that sort of frequent customer little tag on your key ring to get discounts at your grocery store. Sometimes they generate coupons as well, and so a coupon was generated at one of our grocery store outlets in our state.

Many items of direct mail, that I'm going to be able to share with you, over about an 18-month period, a lot of them promoting a free trial or trial with purchase: alternative newspapers, which are typically free in our community; and some point of purchase items as well; some how-to guides; and some sampling packets that were shared.

Again, this is just one of the website pages, an early website that was created to describe the product and how to use it. Here another screen shot of a website showing where the products were available, and just creating an interest and that buzz about the product and where consumers could get them.

Also here are screen shots from some of the

website. And these appear to be comments, just comments from a general tobacco consumer about, oh, gosh, I can't wait till this comes to my state -- again, while it appears to be something that consumers are putting up there, it again was just to generate that buzz and get people excited about trying the new products.

Again, similar comments, mostly positive, generating some interest about the products. Again, a lot of people were talking about how they were going to be able to use these in more increasingly smoke-free outlets and smoke-free environments in our communities.

Social media, and these were some comments that we picked up for some YouTube videos. Again, a few quotes here, and they appear to be mostly from youth, but again commenting on the ability to conceal these products. They're talking about taking more than one. How much will it -- what kind of a buzz can I get, when can an overdose happen, and those sorts of concerns that were available in social media outlets.

This is an example of an email, a direct email marketing promotion, that was seen in January of 2010.

This is an example of a direct mail piece. And again, it's "try one on us" sort of thing. And I did bring some samples; I think sometimes it's helpful to actually see what's being out there. So I'll pass those around so you can see what was sent to the consumers in our area.

A similar ad, but this was an ad in particular which was in the alternative newspapers in the Indianapolis market. Again, these are typically free newspapers around our community, kind of highlighting entertainment in the community.

This next item illustrates a point of purchase education type of tool. I'm going to pass this sample around as well. You'll notice, as was commented earlier -- and this was the earlier product or the earlier packaging of this individual product, how they were difficult to open. And so there was a lot of communication and education that we were seeing about how do you open the product. And so

this is an illustration on how to do that.

The other thing I'm passing around as well, which was this direct mail piece, is not only a "how to open" but it's a "how to use the product," and so by the particular product types, illustrations about the mouth and where to place the product in the mouth to educate the consumer, potential consumers, about where to use them.

Then the last item you're going to see me passing around as well was an actual point of purchase sampling pack. And so if you bought a pack of cigarettes, you were given this sampling pack as well. And you'll notice that the sampling pack was not in a child-resistant container; individual pieces that were easy to open that were given, again, at point of purchase.

So our state and local response, our local coalitions around the state really took this opportunity to raise the awareness about the concern of the product, educating those who worked with youth, getting newspaper articles in their local media as well as newsletter articles because this was

a concern for them as well.

I think that that's one message I'm going to bring with me today, is that not only in the state of Indiana but around the country, there are state and local networks of tobacco control professionals who are able to partner with the FDA in order to be your eyes and ears about what the different types of products are, and not only with dissolvables but with other products as well.

There were some questions just a little bit ago about the surveillance and what do we know? And so we took this opportunity to add a couple of questions in our fall 2010 Indiana Youth Tobacco Survey, just to get a sense about are youth aware of the products and are they trying them.

This slide here gives some comparison to trial of dissolvables, to trial of snus, again, which is a relatively new thing on the market compared to cigarettes, which is traditionally the most popular tobacco item, especially among youth.

Again, you can kind of see -- again, this is just trial in our general population among high

school and middle school youth. But there's that concern about it. About 4 percent of high school males across our population have tried the product.

Then when you drill down either further, among current smokers or youth who identify themselves as a current smoker, what is the trial of the tobacco use? And again, overall use, we have about 10 percent of those youth self-reporting that they had tried the dissolvable product. That even increases up to about 13 percent among males. Again, that's males in middle school level and in high school level as well.

So though it's been discussed so far as this significant concern about dual use of these products, not only across our overall population, but this is specifically about youth. And this is certainly a concern of ours.

Then just to end our story of what Indiana experienced with the marketing of these products, the news article was released in late 2010 about the products being pulled from those three initial test markets to be retooled or repackaged and then

deployed in some new markets. However, in January of 2011, we were still able to find some products still on the shelf in the Indianapolis market area.

So just in summary, I think that we've been able to demonstrate there's a certain significant community concern about when such new products come out. As you've seen, there were a variety of marketing tactics used. A lot of product education on the part of the retail outlets and the company in order to educate about the product to their consumer; and as has been brought up earlier, that concern of dual use and what that means for our population as well.

As the map illustrated, the test market really did extent much beyond the central Indiana or Indianapolis area to the far reaches of our state; and that we do have a vast network of state and community partnerships that are ready to again be those eyes and ears for what's happening at the state and local level for the FDA.

Then just in closing, I think our request is that, from you, to do what you can to regulate these

products. I think we can do a lot, but we can't do it on our own, and that's where you can step in. Thank you.

Committee Discussion

DR. SAMET: Thank you.

Just a first question. In your youth survey, did you obtain any information on how the users became aware of the products?

MS. SPITZNAGLE: No. We didn't ask that.

DR. SAMET: Thank you.

Neal?

DR. BENOWITZ: In your figure where you compare dissolvable snus and cigarettes, you didn't talk about the classic smokeless tobacco. And it's my impression that that's fairly common, in rural Indiana, especially.

How are these products perceived in relation to classic smokeless tobacco?

MS. SPITZNAGLE: While we do have that data, especially about trial and some of the other products, I don't have that with me today to share. I think that, if I can recall, the use of the

dissolvables and trial of the dissolvables is relatively less than some of the traditional smokeless products. But again, I'm sorry, I didn't bring that with me today.

DR. SAMET: Did you look at anyone who had used both smokeless tobacco and these, to get a response of how one compared to the other?

MS. SPITZNAGLE: So if I understand the question, the use of the traditional smokeless and use of dissolvable?

DR. SAMET: Yes.

MS. SPITZNAGLE: We might be able to do some analysis on what we've got with our data, but I didn't bring that with me as well.

DR. SAMET: Thanks.

Ellen?

DR. PETERS: Just to continue, so perhaps unanswerable questions. But I'm curious. You presented data on trying out these products. But what about continuing to use them? What proportion of people who have tried dissolvables versus maybe smokeless tobacco versus cigarettes actually continue

to use them?

MS. SPITZNAGLE: Again, this was our attempt to get some baseline surveillance of the products. These data were collected in late 2010, early 2011, and we have yet to do a follow-up survey. We will likely go into the field again late 2012. So as far as continued use, didn't ask that question. And then again, this was just our first attempt to get some baseline data.

DR. SAMET: Dan?

DR. HECK: Do you have a sense from your surveys or other activities that these products are more accessible to you in terms of improper sales at retail outlets, or are these youth obtaining them through some other irregular means?

MS. SPITZNAGLE: I, again, just didn't look at that information. And at this point, those products were still pretty new in our environment.

DR. SAMET: Bruce?

DR. SIMONS-MORTON: Do you know anything about the demographics or other characteristics of the triers of the dissolvables?

MS. SPITZNAGLE: We would have that data. Again, I think some of the illustrations showed that it's boys, it's males, who have more of an interest in trying them versus females. And some of the racial and ethnic groups, it tended to be white males.

DR. SAMET: Mark and Arnold?

DR. CLANTON: No questions.

MR. HAMM: No questions.

DR. SAMET: Thanks.

Ellen?

DR. PETERS: I had one question about if you have a sense of how much industry effort is put into dissolvables as opposed to cigarettes? So, for example, you said that there's certainly some product education; you passed around some examples. From the anecdote you provided, retailer education might not be very high. But do you have a sense of the relative industry effort that's being put into these?

MS. SPITZNAGLE: That's a really tough question to answer. And I really tried to drill down my comments today on the dissolvables and our

experience with that, so I don't have comparable data to share on how some of the traditional cigarettes or some of the new or novel cigarettes have been marketed.

DR. SAMET: Other questions or comments for our speaker?

[No response.]

DR. SAMET: Great. Thank you very much. When you get your samples back, I want you to make sure that no committee member has taken any of the materials. I was looking at John Lauterbach suspiciously.

[Laughter.]

DR. LAUTERBACH: Dr. Samet, I have plenty in my storage room in my office.

DR. SAMET: Oh, okay. I'm sure you do.

So we're now going to break for lunch. Committee members, please remember there must be no discussion of the meeting topic during lunch either amongst yourselves, with the press, or with any member of the audience.

Thanks to our speakers for covering a great

deal of information efficiently, and we reconvene at 12:30.

(Whereupon, at 11:31 p.m., a luncheon recess was taken.)

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

(12:33 p.m.)

DR. SAMET: If everybody can take their seats, we're going to go ahead and get started.

I think Caryn has a couple of housekeeping, so to speak, announcements.

MS. COHEN: Yes. Thank you. Earlier this morning I asked you to turn down your cell phones. But I'm going to ask everybody to just turn off your cell phones. The microphones in this room are very sensitive and we're getting some feedback. So if you could all just turn off your cell phones.

Also, if the audience members could please refrain from having conversations amongst ourselves. It's kind of a small room, and it interferes with the speakers. So if you feel the need to have a discussion amongst yourselves, please just take that outside. We'd appreciate that.

Finally, if you have preregistered to speak during the public comment period, please be sure to sign up outside, just outside this door. We have one of our CTP staff members, and he has a sign-in sheet

for you.

So that's all I have. Thank you very much.

DR. SAMET: Thank you.

So we will continue with the presentations. And the next presentation is, I guess, returning to Dr. Chen on accidental ingestions.

Presentation - Ii-Lun Chen

DR. CHEN: Hi. I'm Ii-Lun Chen again, a medical officer for the Office of Science. And I'm here to talk about data on accidental ingestions, with the focus on pediatric ingestions, from the publicly available literature.

There has been concern by public health advocates that this newer class of smokeless tobacco products, known as dissolvables, may be more appealing to youth in appearance and flavoring compared to traditional cigarettes or smokeless products, which in turn may lead to increases in harmful accidental ingestions.

It is estimated that 1 milligram per kilogram body weight of nicotine may be lethal for the pediatric age group. Thus, a small handful of

dissolvable tobacco product could have the potential for serious consequences in young children.

The Office of Science reviewers studied data derived from the American Association of Poison Control Centers. The AAPCC is a nonprofit national organization representing the numerous poison centers and other poison-related organizations in the United States. AAPCC owns and maintains the National Poison Data System, providing toxicosurveillance, and more than 50 million case records are held in their database. In the 2009 annual report, there were almost 2.5 million human exposures reported.

Here this graph shows the overall number of exposure events for all age groups associated with tobacco products, as well as nicotine replacement therapy, NRT, products, over time from 2000 to 2009. I present the data on NRT products as nicotine is the main substance of concern associated with potential acute poisoning from accidental ingestions of tobacco products.

There is no denominator. Thus, we are not able to estimate percentage resulting in exposure

events. We have here simply a count of cases reported. These exposure report counts are the number of spontaneous, self-reported calls made to one of the U.S. poison control centers. Exposure events can be intentional or unintentional exposures with potential for poisoning. The numbers here likely underrepresents the true picture given that underreporting adverse events is known to be common.

We see a dip in the tobacco product reports in 2006. Dr. Wang, who's our epidemiologist, noted that, interestingly, there was a simultaneous large dip in the number of exposure events associated with alcohol in 2006, but not in other unrelated products such as glue exposure events.

One of the major changes made in 2006 is that AAPCC restricted reporting to single-substance cases. To explain, that means one case, one substance, and determined to be contributory, to improve precision and avoid misinterpretation. Since alcohol tends to be associated with smoking and drug use, this change in reporting policy may have resulted in this difference between reports of single exposure and

reports of multiple exposures between 2005 and 2006.

Since 2006, there appears to be a steady increase in number of reported exposure events more apparent for tobacco products, but also appears to be a slight increase for NRT products.

Here we are looking specifically at number of tobacco product ingestions for all ages and by specific age groups. Looking at the blue line, which is under the red line here, that represents children under age six years, and the red line is all ages.

So we see that the vast majority, some 90 percent of all cases, involve children under age 6, which equates to approximately 7,000 or more cases per year. In comparison, older children and adults have a much lower incidence of accidental ingestions reported.

The rise since 2006 in number of tobacco product poisonings reflects an increase predominately from the younger children and not from other age categories. In comparison we see the number of reports for NRT products for all ages and for specific age groups. We have significantly less

number of case reports for these products overall.

Interestingly, when you look at the age breakdown among NRT exposures, you will note that there is a different pattern among the age groups as compared to tobacco product ingestions. That is, the young pediatric NRT ingestions do not make up the vast majority of exposure events, as seen for tobacco products, although they comprise about maybe half.

Exposures seem to be more similarly prevalent in both the young and older children, as well as adolescents, but least for adults. Similar to the trend in tobacco products, there does seem to be a rise in case reports over the past decade.

Now we go back to looking at both tobacco product and NRT product exposure cases over time. Please note that the Y axis is logarithmic.

We focus here on the more recent report from 2005 to 2009. Prior to 2005, all tobacco product exposures were lumped in one category. As of 2005, we have more information on specific subcategories of tobacco product ingestion. The subclass code is seen in the indexed box to the right-hand side.

At the top, by far, we see that the most frequently reported exposure is for cigarettes, almost 10,000 reports of cigarette ingestions alone. Then clustered in a group are NRT, chewing tobacco, and unknown tobacco products, all these products having around a thousand reports submitted per year. Then, in pink -- well, sorry, it doesn't really come out as hot pink here -- we see the smokeless product cases, numbering around 800 cases per year.

This graph focuses on cases of non-cigarette tobacco product exposure specifically for the under-age-6 category. The dissolvables are represented within the pink line among smokeless reports. So we see that for 2009, there are around 400 cases involving young children ingesting smokeless products, including dissolvables.

In these reports depicted on the previous slide, the category "smokeless" includes the following products: Ariva, Camel orbs, Camel sticks, Camel strips, dissolvable tobacco not otherwise specified, Iqmik, which is a form of homemade smokeless tobacco used by Alaskan natives, snuff,

general formulation, as well as Stonewall.

Of all the tobacco exposure reports submitted in 2009, only half include information on the severity of adverse event outcome. Of these reports with outcomes, about 60 percent of outcomes had no signs or symptoms as a result of the exposure, but 40 percent did have at least minor signs or symptoms as a result of the exposure. There were limited numbers of accidental ingestions with major health consequences, as shown.

Definitions for reports in the AAPCC are as follows:

No effect, I think that's pretty obvious that the patient did not develop any signs or symptoms as a result of the exposure;

Minor effect, the patient developed some sign or symptom as a result, but minimally bothersome and generally resolved, such as self-limited GI symptoms, drowsiness, skin irritation, transient cough;

Moderate effect, the patient exhibited signs or symptoms as a result of exposure that were more pronounced, more prolonged, or more systemic in

nature; usually some form of treatment was indicated; symptoms, however, should not be life-threatening, and no residual disability should be remaining. Corneal abrasion, high fever, disorientation, isolated brief seizure, are some examples, but all need to respond to treatment;

Major effect, the patient exhibited sign or symptom as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement, such as repeated seizure, cardiac or respiratory arrest, or esophageal stricture; and

Death, the patient died.

As I wrap up this presentation, I bring you back to this graph reporting number of total exposure events reported to AAPCC in 2009. It was only in 2003 that Star had both Ariva and Stonewall products on the market as the first dissolvable tobacco products. More recently, in 2009, RJR started test-marketing their Camel line of dissolvable products.

It will be informative to know what the

upcoming annual reports show in terms of number of case reports for this class of products. The existing data does show that there appears to be an increasing trend in both tobacco product and NRT product exposures.

In the most recently reviewed AAPCC annual report, which was 2009, the number of tobacco product potential poisoning events was around 8500 reports, with over 500 smokeless reports, which include dissolvable tobacco products; 421 of the smokeless events involved young children less than age 6.

My presentation was limited to publicly available exposure reports sent to AAPCC between 2000 to 2009. As an addendum, I did look at the 2010 report, which was just released last month, and the number of smokeless exposure events is in the similar range.

In addition, I would like to alert you to a recent serious accidental ingestion involving a young child that was reported to a local poison control center. In this case, a 2-year-old child was thought to have ingested one or more dissolvable tobacco

tablets. The child was taken to an emergency room with hypothermia, dehydration, nausea, vomiting, and lethargy.

The patient was treated and observed overnight. Apparently, the child's father habitually removed dissolvable products from a child-resistant packing they originally came in and stored them in a screw-top container. When the child was left unattended in a room with the container, the accidental ingestion occurred.

In conclusion, as a regulatory agency with the mission to protect public health, we should work towards reversing the trend of increased numbers of accidental exposure and preventing additional cases of potential tobacco and nicotine poisonings as best as possible.

I'd like to acknowledge Dr. Wang, who's the epidemiologist in our Office of Science.

Now we have Dr. John Boja from the Consumer Product Safety Commission, here to present you information on the Poison Prevention Packaging Act, in consideration for special packaging and how

special packaging has impacted accidental ingestion for other products under their regulation. Thank you.

Presentation – John Boja

DR. BOJA: Hi. I'm John Boja. I'm from the U.S. Consumer Product Safety Commission. That said, being I'm with the government, I have to remind you that the comments that I make are those of my own and may not represent those of the commission. Generally, I put in the comment now that I deserve a raise; the commission may not think so. So that's one of the things that we differ on.

[Laughter.]

DR. BOJA: What I will address today is the Poison Prevention Packaging Act. Oh, the other issue we differ on is I need more staff. They don't agree.

[Laughter.]

DR. BOJA: The Poison Prevention Packaging Act is to protect children from serious personal injury or harm resulting from handling, ingesting, or using hazardous household substances.

A household substance is something that's

commonly produced or distributed for sale for consumption or use around the home, stored in the home, and which is defined by the Federal Hazardous Substances Act, the FHSA, as a hazardous substance, or defined as a drug, as defined under the Food, Drug & Cosmetic Act, or a substance intended for use as a fuel or an illuminating fluid that's in a portable container used for heating, cooking, or refrigeration of the home.

A package means the immediate container or wrapping around the substance. So that's what's actually touching the substance. We do not allow somebody to take, say, a unit dose package and stick it into a special packaged bottle. I will use the term "special packaging" rather than "child-resistant," as you'll see later that our packages are not only required to be hard for children to get into, but they have to be easy for adults to get into as well.

One of the findings we have to make in order to require a substance to be required to be in special packaging is availability of the substance

would cause harm to a child. Children don't read labels, so we can't label away a hazard. We require special packaging to give parents an extra buffer or an added time to remove that substance from the child's possession in order to prevent or reduce the ingestion that a child may have.

We also have to be able to find that the packaging is technically feasible. So it's something that they can make and not something that we just dreamt up to do that. It has to be practicable; that is it has to be made by modern mass production methodologies, and it has to be appropriate for the substance. There are some substances that you can't put in certain packages because they would melt the plastic or they would interfere with the child-resistant features.

Special packaging is designed to be significantly difficult for adults under the age of 5 to open or obtain a toxic amount within any reasonable amount of time, and not difficult for normal adults to use properly. We really shudder when people use the term "childproof." There is no

such thing as a childproof package out there. You give a child enough time, they will open it.

We do have incident reports where parents, the child was in the back seat of the car, was being noisy, they handed them a bottle of pills to use as a rattle, and then our report was that the child actually opened them. And again, if you give a child a lot of time, they will do that.

We also require that the package will not be difficult for normal adults -- read that now as senior adults -- to open. And the reason being is if an adult cannot open a package properly, the cap will be left off; or that package will be opened once and left open; or, God forbid, it will be transferred to a baggie or just left out on the counter. So we require that the package not only be difficult for a child to open, but an adult must be able to open that package as well, again, within a reasonable amount of time.

Nothing in the act allows us to specify a specific package design. So we can't tell a manufacturer, you've got to use special packaging,

and it's got to be a unit dose package. We can't do that. They can use whatever special packaging is available.

We cannot specify the package content or the quantity. So while we may think it's not a great idea to put a thousand tablets in a consumer package or 2,000 or whatever, we're not allowed to do that by our statute.

Some of the substances that are included in 16 CFR Section 1700.14(a) include acetaminophen; aspirin; controlled drugs; dibucaine; diphenhydramine; ibuprofen; iron-containing drugs and dietary supplements; ketoprofen; lidocaine; loperamide; methyl salicylate; minoxidil; mouthwash that contains ethanol; naproxen; oral prescription drugs -- and I emphasize oral -- when this was put into place, they had no idea that transdermals and intranasals would be in households, so right now we're limited to oral prescription medications -- and OTC switch drugs.

So any medication that was switched before January 29 of 2002, if they made the application to

the FDA to switch, they are grandfathered in. Anything that was switched after that must be in child-resistant packaging unless the manufacturer would petition the CPSC for an exemption.

Some of the substances that are required to be in special packaging include ethylene glycol; fluoride; furniture polish; glue removers that contain acetonitrile, hydrocarbons, kindling and illuminating preparations; methacrylic acid; methanol; again, mouthwash that has ethanol in it; permanent wave neutralizers that either have sodium or potassium bromate; sodium and potassium hydroxide; solvents for paint and other surface coatings; sulfuric acid, unless it's in a storage battery; and then turpentine.

We have exceptions. Those include products that are not used around the household; institutional use products, medications that are given in a hospital or in a nursing home. Recently, the commission had to deal with the question of assisted care facilities; are they nursing homes? And the commission issued an opinion stating that if the

nursing home or assistance living facility had a central pharmacy and dispensed medications for the patients to take back to their living quarters, then it requires special packaging because that living quarter would be much akin to a household. If the medications were given out to be taken immediately, then they were not required to be in special packaging.

We have a professional use exemption, so if things are sold only to professionals, they are not required to be in packaging. This cannot be gotten around by putting a label on a substance that says, "For professional use only," and then selling it in Home Depot. That needs to be in special packaging, and we do monitor sales of packages and see how they are marketed when we determine whether or not a product is in violation.

Bulk prescription drugs that are meant to be repackaged by the pharmacist are not required to be in special packaging. And Section 4 of the PPPA allows a limited use of noncompliant packaging. A patient may request non-child-resistant or non-

special packaging at a pharmacy. The physician may prescribe non-special packaging when they write the prescription.

Then we have certain exemptions for medications, like erythromycin that has low toxicity is not required to be in special packaging. Sublingual nitrates are not required to be in special packaging, again because we don't want to limit the availability of that drug in an emergency situation.

Over-the-counter drugs, we allow an exemption of one size and one size only for a specific substance that was put in there for people that have trouble opening special packaging. They have to have a special label on it, and this is the only label that we are allowed to mandate. They have to say that that package is non-child-resistant.

It cannot be their most popular selling size, so we do look at sales records. And there are certain substances -- for example, drain cleaner -- that cannot use that exemption because that's a very hazardous substance, and there's no need for someone to really require access to that

product if they don't need to.

The packaging test method consists of one to four panels of 50 children. Their ages range from 42 to 51 months, and the exact breakdown is 42 to 44 months, 45 to 48 months, and then 49 to 51 months.

There's a restriction on the number of children that can be tested by a given tester so we don't introduce bias. There's a site restriction, again so we don't stratify our sample. We don't want all the kids from one group or another. There's a five-minute demo -- or a five-minute test. The package is given to a child. They are asked to open it. If they do not open it within that five-minute period, there's a demonstration in which the tester will open a package in front of them, much like a child would be able to observe their parents opening a package. However, there are no overt actions given to the child. It's not said, "Well, this is how you can open it."

They are then told that they may use their teeth, if they have not already done so, to assist them in opening the package. There's another five-

minute test, and if the package is not opened within that second five-minute period, the package is deemed having passed.

There's a sequential pass/fail table that I'll show you in the next slide. The minimum requirement for packages is 80 percent after 200 children.

As you can see here, we use one test panel of 50 children. It's an outright pass if zero to 5 children open that package within the full 10-minute period. That's about a 98 -- no, it's 95 percent. It goes down to 80 percent, as I mentioned, when we test 200 children.

A unit package is different than a regular bottle packaging, and we acknowledge that. And it's a little different in the way we look at a failure. You open a bottle, or a test failure could be simply that -- when the seniors use it, we'll talk about a special case there. But if they open a bottle, they can gain access to everything. With unit packaging, you have to open each individual unit.

A test failure with a unit package is a child

who opens or gains access to the number of individual units that would constitute the amount that would cause serious personal harm or injury to a 25-pound or an 11.4-kilogram child, or access to 8 or more units.

The difference here is when you open a bottle, you've got everything and you can tell it's open. We say here, "opens or gains access," and that's become very important now with our oral disintegrating tablets, the rapid dissolves, because if a child just merely pulls back the foil a little bit without actually getting the tablet out, they could salivate into the blister cavity and then suck out the contents. So we would count that as gaining access, and just a pinhole would be counted as a failure in the case where we have an oral disintegrating tablet.

As I mentioned, special packaging would not be used by adults if they couldn't open it. We test, for seniors, 100 adults aged 50 to 70 years old. Just as we saw with the children, there's both a sight and tester restriction.

Unlike the children, which used a 50/50 distribution for gender, we use a different distribution with the seniors. We use a 70 percent female distribution, again looking at the population, and then also knowing that as people get older, females generally are the caregivers.

There is a five-minute test. The senior is told to look at the package and then follow the directions and open it. After that period, they are given an identical package, and they are given a 1-minute period to open the package. The first five minutes is considered a learning exercise, and if they can't open a package within one minute, knowing how to open that package, the likelihood that they'll not use it is greatly enhanced.

If a package is not opened by a senior, they're given a screening test. And a screening test consists of two dissimilar non-special packages. So they're given a package that has a regular threaded closure, just to twist the top off, and they're also given a snap closure, where you just pop the top off.

If they cannot open either one of those

packages, they are eliminated from the test because if they can't open regular packaging, they're not going to be able to open special packaging. We require a 90 percent effectiveness with the senior test.

Before we went to a senior test, we looked at adults. So we still have a portion of our protocol in place before the protocol revision went into effect, where we looked at older people.

We look at 100 adults here. This is only used for metal cans that have a metal top on them. You used to be able to see aerosol cans that way. There is one five-minute period, and again, 90 percent effectiveness is required. And you can see the ages here are 18 to 45 rather than the seniors.

Physician samples, we do not require them to be in child-resistant packaging because they're oral prescription drugs that would require packaging; however, Section 4 of the PPPA allows a physician to request non-child-resistant packaging in their order.

Since a physician is the one that is not only

prescribing that drug but also the one dispensing the drug, they are then taking the responsibility of providing non-child-resistant or non-special packaging to the patient. We encourage firms to put samples in child-resistant packaging, but we cannot require them to do so.

This provision does not apply to over-the-counter drugs because over-the-counter drugs are not issued upon the order of a physician. So you cannot give out samples of an OTC drug in non-special packaging.

With the advent of the Consumer Product Safety Improvement Act, or the CPSIA, we require that special packaging have a certificate. Now they have to issue a certificate of conformity stating that the package that they are providing to consumers has been tested and it does pass. I'll kind of skip through that rather quickly.

They have to say that it meets the performance specifications that are in our regulations. They have to identify the product, the importer, and then who's maintaining the test records

and where it was tested.

We have additional information on our Web page if you would like. Also on that page are some different packaging designs that you're more than welcome to look at. We do require that in order for a firm to have those designs on our website, that they do provide data so that we can be assured that they were indeed tested and they indeed passed the special packaging regulations.

That's our contact information, and thank you very much for inviting me.

Committee Discussion

DR. SAMET: Thank you, and thank you both for your presentations.

Let me open it up for discussion of these presentations about poison and product packaging.

Bob?

DR. BALSTER: I have a question for Dr. Chen. I can appreciate very much why you show the poison control data the way you do. But it seems logical that the number of poison reported cases like this is going to be correlated with the basic product

availability in the market, and so that as product availability changes, those numbers would change.

I'm wondering if there's any suitable denominators that could also be applied to those data like, for example, units sold or something like that; if there's any consensus about denominators that would give you a better relative risk assessment.

DR. CHEN: Yes. We don't have marketing sales numbers. I wish we could get access to that, and that could be helpful. As you said, it depends; knowing the general distribution of how much product is on the market and how many cases would be helpful, but I don't have that information right now.

DR. SAMET: I think I know the answer. In terms of the way that information is captured by the poison control centers, are specific products ingested named?

DR. CHEN: They can be. It's possible that if the parents or the reporting figure know the name of the product, that can be recorded and we can get access to that. And we also can get, for example, state-specific. And so it would be interesting if

products -- depending on availability, test markets, we can look into any trends. That could be useful information.

DR. SAMET: I guess the question is -- because what you showed us are these very nonspecific categories around smokeless, for example, that would not have the resolution that might be wanted --

DR. CHEN: Right. In general, for the publicly available information, that specificity is not available to us. That would have to be purchased from the AAPCC. So in order to get state-specific information or product-specific information, we would actually have to ask for special permission to obtain that sort of data. But what's available in the literature in terms of the annual reports is just total number and some of the demographics in terms of age group categories.

DR. SAMET: I guess the question would be -- related question, that if you wanted to know what was in the records, you would probably actually have to go review hard copy or whatever the

database -- so where would information reside?

DR. CHEN: Yes. There is a database, and in order to get access to the database, you would have to purchase the rights to the information.

DR. SAMET: So this is something that you could take another step, at least exploratory, by having the data at that level to understand what might be there?

DR. CHEN: We could. The cost is substantial, but we could. If we needed to, we could.

DR. SAMET: And the costs are how much?

DR. EVANS: So you said a million dollars, Kathy?

DR. CHEN: A million dollars, for us to access the database, the cost given to us is that amount.

DR. EVANS: It's for 10 years of data, though. That cost includes 10 years of data.

DR. SAMET: Okay. Interesting.

DR. EVANS: Apparently, we will be purchasing that.

DR. SAMET: Other questions for the presenters? I do have some questions for the CPSC, but yes, Ellen?

DR. PETERS: I had a question for the second speaker. I was just curious. Consumer goods companies, at least in the past, used to not be able to put products like detergent in containers that looked like something kids would ingest.

So, for example, you weren't allowed to do thing like put a laundry detergent-like chemical in something that looked like the pint milk containers that children used to drink in elementary schools. I don't even know if they do that any more.

But are there rules like that within what you talked about?

DR. BOJA: Yes. There's rules that require -- that prohibit the packaging of substances in packages that a child would find overtly attractive. We have taken action against a vitamin manufacturer that I think they put the vitamins in a figurine that looked like Yogi Bear. So something a child would play with, we can do that.

DR. SAMET: Tim?

DR. MCAFEE: I have a question about -- essentially, I'm curious. We're looking at a potential problem with dissolvable packaging. But judging from the numbers, it would be a small fraction of the 8- to 10,000 poisoning cases.

But there's something like 8,000-plus poisonings associated with cigarettes. So I'm just curious in terms of the authority of your agency, why wouldn't you or would you consider actually looking at cigarette packaging and requiring -- it seems like -- does it not meet some requirement relating to your regulatory mandate? And if so, why would dissolvables --

DR. BOJA: I do not believe that cigarettes are under our authority.

DR. MCAFEE: Would dissolvables be under your authority?

DR. BOJA: I would have to check with our Office of the General Counsel to find out. They might be, but I'd have to double check.

DR. MCAFEE: I would be hard-pressed to

understand why one would and one wouldn't. And I guess if they aren't, I'm curious what the relevance is.

DR. CHEN: This is my personal understanding of the situation, is that tobacco products were exempt from these regulations. And at the time, they were not considered a toxic household substance. And so they were exempt from these regulations. That is my understanding, that tobacco products do not fall into this regulation.

DR. MCAFEE: So does FDA have some other form of authority? Again, I'm trying to understand for the committee's sake what the -- if you don't have authority and if FDA didn't, what the relevance would be to the discussion.

DR. CHEN: So CPSC has different authorities and laws that they follow, and CTP would have different statutory regulations and laws to follow. And so if that is a consideration, then it's possible that we could consider it further. But again, this topic is limited to dissolvable tobacco products, so that would be another discussion.

DR. SAMET: Just to follow up, though, so I think we heard CPSC has no authority over tobacco. Clear answer. And then I guess I'm not sure whether I did or did not hear a clear answer on whether FDA, under the Act, has any jurisdiction over product packaging, and I guess for the dissolvables in particular.

DR. CHEN: I would have to clarify that with our supervisory members. But we may have ability to develop regulations surrounding that. But I'm not clear at this time.

DR. SAMET: David?

DR. ASHLEY: I know there are people in the audience that will probably start screaming when I start talking. But from what my read is -- and this is not -- this is for sure not a legal evaluation of what the statute says. When I look at the description of the authorities we have under product standards, they're very broad. There are a lot of things that are included in that. And it could very well be that we have that authority under our product standard authorities. Now, again, we're going to

have to do a legal analysis or someone will have to tell me exactly if that's correct or not. But our authorities under product standards are very broad in that sense.

DR. SAMET: Bob?

DR. BALSTER: So do we know whether or not the current packaging for the dissolvable products would meet that CPSC standard that Dr. Boja described?

DR. BOJA: Since it's not a substance that we really regulate, we haven't asked to see that test protocol data. I understand that they do advertise it as being in child-resistant packaging. But without seeing that actual data, I could not comment on it.

DR. SAMET: Bruce?

DR. SIMONS-MORTON: Is there an example of FDA regulating packaging for any product?

DR. BOJA: There was a regulation that the FDA had a few years back where the FDA required unit packaging for iron-containing products. And I believe that went to federal court, and they

basically said that the FDA does not have the authority to require special packaging, and that that was given to the CPSC.

DR. SAMET: Other questions? Yes, Fred?

DR. PAMPEL: So for the trend in accidental ingestions of nicotine replacement therapies, there's a fair amount that involve 19-year-olds and over. Is that overdoses? They take more than they really need? Or is it accidental, and they're not sure what they're taking?

DR. CHEN: There could be both, actually, unintentional and intentional. I was focusing on the younger children, so I'd have to go back and take a look to see if there was information on how many of those were intentional for the adolescent and older age group.

DR. SAMET: Mark? Arnold?

DR. CLANTON: No comment.

MR. HAMM: No comment.

DR. SAMET: Thank you.

Let me see if there's any other questions about these. If not, we're going to have an

unanticipated break, unless we want to make idle conversation. I think our next speaker is scheduled for 1:30. She's in the parking lot.

So any other questions? Yes, Bruce again?

DR. SIMONS-MORTON: So there is some regulation for tobacco packaging, is there not? And who does that?

DR. SAMET: Dave, do we have anybody who can speak to that? I mean, we know about numbers of cigarettes and warnings, but is there anything else that you can comment on?

DR. EVANS: I was just telling David, we can get someone here from, I guess, the compliance office. I don't know that we can speak to that.

DR. SAMET: Bob?

DR. BALSTER: And just since we -- again, the issue about not having available information to put a denominator on poison control data, I mean, where would that information be? How would FDA be able to obtain the information on, say, product sales for putting a denominator on poison control data?

DR. SAMET: Dr. Chen, any comments?

DR. CHEN: I think there is some marketing tracking information available. And again, it may have to be purchased, but it is a possibility that that's some information that can be obtained to give us a ballpark figure.

DR. EMERY: Nielsen Company, that monitors TV ratings, also monitors purchases at the point of sale in all sorts of different types of outlets. And those are available data if you have the money to buy it.

DR. SAMET: Anything else?

[No response.]

DR. SAMET: Thank you. So I'll give CPSC some gratuitous advice. So I was interested that the senior age group is 50 to 70.

[Laughter.]

DR. SAMET: Given the changing demographics of the United States, you may need to rethink that.

DR. BOJA: Although there may be some --

DR. SAMET: Take that back, please.

DR. BOJA: There may be some chair bias in that.

[Laughter.]

DR. SAMET: Unrevealed.

So why don't we -- I think we'll just be on sort of a lull here until our next speaker comes. And thank you both for your presentations.

(Whereupon, a brief recess was taken.)

DR. SAMET: If everybody could take their seats, please, we're going to start up again. And if I could just remind everybody who is planning on speaking in the open public session to please sign up outside and confirm that you're here and plan to speak.

David?

DR. ASHLEY: I just wanted to mention to everyone that what we're about to have is a review of the peer-reviewed literature. A lot of the papers that will be talked about have been talked about in other sessions, other parts of this. So don't be confused. And if you think to yourself, haven't I already heard about this paper, yes, you have.

So I just wanted to clarify that, again, RTI did exactly what we asked them to do. And some of

these papers you have already heard about, but we wanted to get a full summary of what is in the peer-reviewed literature.

DR. SAMET: Go ahead.

Presentation – Linda Brown

DR. BROWN: All right. So as Dr. Ashley said, I'm going to be providing a review of the peer-reviewed literature related to dissolvable tobacco products.

This slide presents an overview of my talk. First I'll describe the purpose of the presentation, then the approach used to identify articles and the findings, presented as a summary of each reviewed article. And then I'll be happy to answer any questions at the end of my talk.

The purpose, as we have done for other talks, is to inform recommendations of the Tobacco Products Scientific Advisory Committee by presenting a summary of the peer-reviewed literature on dissolvable tobacco products. And we also have the disclaimer that although this work, the work reported, was done under contract with FDA's Center for Tobacco

Products, the content and conclusions of this presentation are those of RTI International.

As of December 16, 2011, 25 peer-reviewed articles regarding dissolvable tobacco products were identified by FDA using PubMed, Science Citation Index, Social Sciences Citation Index, Google Scholar, PsychInfo, and Business Source Corporate. Search terms included dissolvable tobacco, novel, strip, stick, pellet, orb, toothpick, and brand names of products by manufacturers thought to market dissolvable tobacco products.

The identified articles were submitted to RTI International and were reviewed by me and another research epidemiologist. Of the 25 articles, I will review 21 of them today. Since TPSAC is not being asked to address use of dissolvable tobacco products as cessation aids or potential modified risk tobacco products, I will not be presenting information on four articles primarily related to those topics.

My summary will highlight the information available on dissolvable tobacco products and will be presented in chronological order. All articles were

published during 2006 to 2011, with the exception of one article published in 1991. And as I just stated, one article was published in 1991.

Please note that article titles are listed at the top of each slide and funding source at the bottom. However, in the interest of time, I'll be referring to each article by author.

Hasenfratz and Battig conducted a randomized crossover study of 12 healthy female overnight abstinent smokers aged 20 to 39. The study objectives were to assess the amount of nicotine that could be absorbed from the 4-milligram nicotine-containing toothpick and investigate the resulting physiologic and subjective effects compared to the 4-milligram nicotine chewing gum.

The authors found that nicotine-laden toothpicks can provide nicotine at a rate equal to or faster than commercially available nicotine gums. However, the potential advantages of the toothpicks -- one, dental care, and two, as a substitute for the manipulative component of the smoking act -- remain to be verified in further

experiments.

Two articles were published in 2006. Caraballo et al. conducted a focus group of 140 current smokers aged 30 to 50 in 16 focus group sessions. The study objectives were to understand how smokers learned about potentially reduced exposure products, PREPs, including the dissolvable product, Ariva; reason for trying; which ones they tried; first impressions; and reasons for continuing or discontinuing use.

The authors reported that Ariva was tried by only 12 percent of subjects, whereas Eclipse, a PREP test-marketed in the focus group areas, was tried by 90 percent. The authors noted that, one, most of the smokers did not like the PREPs and would not recommend them; and two, those who used PREPs did so occasionally while continuing to smoke their regular cigarettes. They further noted that the health risks for combined use of PREPs and cigarettes are unknown.

Stepanov et al. conducted a basic science study comparing tobacco-specific nitrosamine, TSNA, levels in six new tobacco products, including the

dissolvables Ariva and Stonewall, with levels in nicotine replacement products and conventional smokeless tobacco and cigarettes. They found that TSNA levels were lowest in Ariva and Stonewall and highest in Exalt snus. The authors noted that levels in Exalt were comparable with those found in some conventional commercial brands of smokeless tobacco.

Three articles were published in 2007. The objectives of a review article by Hatsukami et al. were to describe the extant literature on newer smokeless tobacco products directed at smokers, including Ariva and Stonewall, and the current literature on the toxicity of these products.

The authors found that, one, TSNAs are highest in the conventional and most popular oral tobacco products, that is, Copenhagen and Skoal, and lowest in Ariva and Stonewall; and two, concentrations of the tobacco nitrosamine, NNAL, were similar for Ariva and medicinal nicotine, Commit, and substantially lower than in cigarettes and other brands of noncombusted oral tobacco products.

The authors noted that, "No data are

available on the health effects of the newer, low nitrosamine, noncombusted oral tobacco products, including Ariva and Stonewall, aimed toward cigarette smokers."

Kotlyar et al. conducted a randomized crossover study of 10 men aged 20 to 49 who had used Copenhagen smokeless tobacco daily for at least one year. The study objective was to compare the pharmacokinetics and subjective responses of three new smokeless tobacco products, including Ariva and Stonewall, to moist snuff and medicinal nicotine lozenges.

The authors found that use of Ariva and Stonewall results in lower nicotine concentrations and equivalent or lower reductions in subjective measures compared with medicinal nicotine. However, they noted that the likelihood of PREPs, such as Ariva and Stonewall, cause diseases associated with smoking or smokeless tobacco use -- for example, cancer and cardiovascular disease -- is largely unknown.

O'Hegarty et al. conducted a focus group

study of 140 current smokers aged 30 to 50 in 16 focus group sessions. The study objective was to describe reactions to print advertisements and promotional materials for a number of novel PREPs, including Ariva.

The authors found that, one, 90 percent of participants reported trying Eclipse, whereas only 12 percent had tried Ariva; two, many participants did not view Ariva as a replacement for cigarettes but rather as an alternative product to use in situations in which they could not smoke; three, many of the participants initially thought that the Ariva promotional material was for a non-tobacco product, for example, breath mints, chewing gum, or antacid; and four, men and women in all groups were strongly offended by the health warning about gum disease and tooth loss.

The authors noted that as more novel products are introduced into the market, it is important for the public health community to monitor smokers' perceptions about these products.

Three articles were published in 2008. Blank

et al. conducted a clinical laboratory study using 10 overnight abstinent cigarette smokers aged 18 to 50. The objective was to examine the nicotine delivery, cardiovascular profiles, and subjective effects of Ariva.

The authors found that Ariva, one, delivered active doses of nicotine when 2 or 3 tablets were used simultaneously; and two, suppressed several symptoms of tobacco abstinence or withdrawal to varying degrees. However, they noted that Ariva's nausea-inducing and other adverse effects -- for example, increased health rate, dizziness, and headache -- may limit acceptability.

Gray et al. conducted two clinical laboratory studies, N=13 and N=19, among smokeless tobacco users aged 18 to 50. The objective of the studies was to adapt efficient and reliable methods to examine the withdrawal, suppression, and toxicant exposure associated with PREPs, including Stonewall, to understand the short and longer-term effects.

The authors found that, one, neither Stonewall nor the placebo condition produced

significant increases in plasma nicotine at any use episode; two, compared with own brand of cigarettes, Stonewall was associated with lower levels of urine cotinine and NNAL; and three, abstinence symptoms generally did not differ across tobacco conditions.

The authors noted that there is a need for comprehensive standardized evaluation strategies for Stonewall and other PREPs that include reliable and efficient laboratory methodology that would be performed prior to release to the consumer and be overseen by a regulatory body that controls PREP availability and marketing.

Slater et al. conducted a national survey of 4,126 tobacco retail stores. Sites were selected using the sampling frame from the Monitoring the Future Study. The study objectives were to examine and understand the availability and marketing of PREPs, including Ariva, in selected retail stores, and also the price of these products versus premium brand cigarettes.

The authors reported that, one, Ariva was carried by 2.5 percent of stores; two, the mean price

for Ariva was lower than for Omni and premium priced cigarettes, Marlboro and Newport; three, there was only one promotional offer for Ariva; and four, Ariva was more likely to be available in gas or convenience stores and drugstores in suburban areas, and in the South, and less likely to be available in neighborhoods with a higher than national average of Hispanics.

The authors noted that Ariva and Omni have a long way to go in terms of availability and marketing to make them viable and competitive alternatives to or substitutes for cigarettes.

One article was published in 2009. Parascandola et al. used data from NCI's Health Information National Trends Survey, HINTS, of more than 6,000 adult respondents in 2003 and more than 5,500 in 2005. Their objective was to provide national estimates of awareness and use of PREPs, including Ariva and Stonewall, by brand and consumer interest in using.

The authors found that 45 percent of subjects had heard of at least one PREP product; 4.8 percent

had tried one. Awareness was 5.4 percent for Ariva, but less than 1 percent for Stonewall. Awareness and use were substantially higher among current smokers.

Interest was higher in females and non-Hispanic whites, among daily and heavy smokers, and those not considering quitting. Smokers interests in PREPs were more likely to rate their perceived lung cancer risk high and to worry about developing lung cancer. The authors noted that health-conscious smokers may be essentially vulnerable to PREP marketing messages.

Six articles were published in 2010. Blank and Eissenberg conducted a clinical laboratory study of 21 smokers aged 18 to 55. The study objective was to measure the toxicant exposure and abstinence symptoms associated with the use of orally administered noncombustible PREPs, including Ariva, using positive own brand cigarettes and negative No-T/no-tobacco control conditions.

The authors found that Ariva was associated with lower acceptability ratings, carbon monoxide, and urine cotinine levels, and higher abstinence

symptom ratings relative to OWN, and higher levels of NNAL relative to No-T.

The authors noted that although these noncombustible products reduce exposure to carbon monoxide, their ineffective abstinence symptom suppression and low acceptability may limit their viability.

Carpenter and Gray conducted a randomized trial among 31 cigarette smokers aged 18 to 65 not interested in quitting. The study objective was to test smokeless tobacco, including Ariva and Stonewall, among smokers unmotivated to quit and its influence on smoking behavior and cessation.

The authors found that use of Ariva and Stonewall led to a significant 40 percent reduction in cigarettes per day, with significant increases in self-efficacy to quit and readiness to quit smoking either in the next month or within the next six months, with no significant increases in total tobacco use. No such changes were observed among smokers maintained on conventional cigarettes.

The authors noted that Ariva or Stonewall

could serve as a catalyst to increase motivation to quit among smokers not wanting to quit. They recommended that a large prospective randomized clinical trial be conducted to assess long-term use.

Cobb et al. conducted a clinical laboratory study of 28 overnight abstinent cigarette smokers aged 18 to 55. The study objective was to assess the acute effects of noncombustible PREPs, including Ariva.

The authors reported that Ariva delivered less nicotine than own brand cigarettes and did not expose users to carbon monoxide or increased heart rate. However, it failed to suppress tobacco abstinence symptoms as effectively as cigarettes.

The authors noted that comprehensive premarket evaluation of a process designed to minimize toxicant exposure and maximize suppression of abstinence symptoms may be the most productive method for realizing the public health potential of Ariva and other PREPs for tobacco users.

Connolly et al. used data on over 13,700 cases of tobacco ingestion among children less than

six years of age from the National Poison Data System, 2006 to 2008. The study objectives were to examine child poisonings nationwide resulting from ingestion of tobacco products, and to assess the potential toxicity to young children of Camel orbs, a novel smokeless tobacco product.

The authors reported that, one, greater than 70 percent of ingestion cases involved infants less than one year of age; two, ingestion of chewing tobacco and snuff was secondary in frequency after cigarettes; and three, one case of ingestion of orbs by a three-year-old child was reported by the Oregon Poison Control Center in 2009.

In addition, orbs tobacco pellets were analyzed and found to contain 0.83 milligrams of nicotine and a pH of 7.9, resulting in 42 percent of the nicotine available in the unionized form compared with 10 percent for cigarettes.

The authors advise that public health authorities study dissolvable nicotine products to determine the appropriate regulatory approach in light of their novelty. The discreet form of orbs,

which are the size of a Tic Tac, might make ingestion of nicotine easy and attractive for adolescents; and potential harm, the average pH of an orbs pellet is more alkaline that cigarette tobacco, which might enhance toxicity.

The objective of a review article by Piano et al. was to review and summarize the scientific evidence regarding smokeless tobacco use and its potential cardiovascular risks to inform policy related to tobacco control and strategies related to tobacco harm reduction.

The authors reported that Ariva and Stonewall have nicotine content ranging from 0.6 to 3.1 milligrams, and dissolve in 3 to 15 minutes. Other new smokeless tobacco products, such as Camel orbs, contain 1 milligram of nicotine per orb, and Camel sticks, the size of the toothpick, contain 3.1 milligrams per stick.

The authors noted that long-term use of smokeless tobacco products may be associated with an increased risk of fatal MI and stroke and some cancers and oral disease. However, no data were

presented on cardiovascular or other health risks related to the use of dissolvable tobacco products.

Schwartz et al. conducted a basic science study using 75 rats 4 to 6 weeks of age. The study objective was to assess long-term mucosal changes induced by daily use of four different smokeless tobacco formulas, including Stonewall, and these were studied side by side and applied under identical protocols in an animal model.

The authors noted that although all smokeless tobacco products produced varying degrees of acute, subacute, and chronic inflammation in the stoma, products such as Stonewall with lower levels of TSNAs and unprotonated nicotine caused less dysplasia, consistent with the model that tobacco with low levels of nitrosamines might potentially induce fewer cancers in human users.

Five articles were published in 2011. Hatsukami et al. conducted a randomized trial among 99 smokers interested in quitting. The objectives of the trial were to assess the preference of five oral tobacco products, including Ariva and Stonewall, that

differed in formulation and dose of nicotine, and the effects of selected products during the two-week trial.

The authors reported that with the exception of general snus, a high-nicotine product not preferred by any smoker likely due to taste, there were no significant differences among the other four tobacco products. However, products with higher nicotine levels, such as Stonewall and Camel snus, were rated more highly -- that is, more satisfaction and more craving relief -- than products with lower levels of nicotine, such as Ariva and Marlboro snus. Camel snus was associated with significantly higher rates of abstinence than Ariva and Stonewall.

O'Connor et al. conducted a trial of 67 smokers not interested in quitting and not currently using any other nicotine or tobacco products. The study objective was to examine smokers' interest in using a smokeless tobacco or nicotine replacement product, including Stonewall as a cigarette substitute.

The authors reported that Commit lozenges was

the most preferred product and Stonewall the least, with only 12 percent of subjects selecting Stonewall for the 7-day trial. Sixty percent of participants were not at all likely to use Stonewall instead of cigarettes, and zero percent were very likely to purchase in the next year.

Over the 7-day trial, significant declines were seen in cigarettes smoked per day and exhaled carbon monoxide, but there were no changes in use of alternative products or in salivary cotinine levels. The authors noted that smokers currently unwilling to quit may be willing to use alternative products short-term as a temporary partial smoking substitute, and be more willing to use a nicotine replacement over a tobacco-based product.

Rainey et al. conducted a basic science study of four dissolvable Camel tobacco products: Mellow orbs, Fresh orbs, Mellow sticks, and Fresh sticks [sic]. The study objective was to describe the chemical characterization of these four products.

The authors identified nicotine with levels that range from 0.21 to 0.91 milligrams per

dissolvable, and a number of flavoring compounds, sweeteners, and binders in the products. The authors noted that these results are the first to reveal the complexity of dissolvable tobacco products and may be used to assess potential oral health effects.

Romito et al. conducted an audit of a random sample of 81 retailers from six store categories in an awareness-attitude-usage survey of 243 adult never, former, and current smokers. The study objective was to assess the availability, price, and point of purchase promotional strategies for Camel dissolvable sticks, strips, and orbs.

The authors found that these products were carried by 46 percent of retail locations. Overall, 42 percent of consumers had heard of Camel dissolvables, although percentages were higher for former and current smokers. Interest and trial were low in all groups. The authors noted that current retail promotional strategies for these products appear to be targeting a select audience, primarily current smokers.

The final paper is a commentary by Seidenberg

et al. that discusses dissolvable tobacco products marketed in the United States and a new dissolvable product, Revo, marketed in Taiwan that is nearly identical to Camel orbs, sticks, and strips. The authors noted that the results of Camel dissolvables and Revo product analyses, including levels of nicotine and other toxicants, are not yet available to the mainstream scientific community.

They further noted that the introduction of dissolvable tobacco products in other countries highlights the need for improved global surveillance of new tobacco products and for the application of appropriate tobacco control policies and regulations that may include reporting the sale of new products and product ingredients, banning flavors that may appeal to youth, and prohibited unsubstantiated claims.

Now I'm happy to answer any questions, after I take a drink of water.

Committee Discussion

DR. SAMET: Thank you, and thank you for the effort in reviewing these studies.

I actually have a question for Tom. Could you say a little bit about your participants in the studies and how you recruited them? I'm just thinking about the generalizability of findings. And is there any carryover of participants from study to study?

DR. EISSENBERG: So we recruit by advertising around VCU's campus with flyers. We also advertise in alternative newspapers, not the Richmond Times-Dispatch, and in the VCU campus newspaper.

The demographic breakdown is in the paper. I don't have the numbers off the top of my head. We usually do, I think, a pretty good job of getting roughly equal numbers of males and females except for studies of smokeless tobacco users, which are almost exclusively men. And inasmuch as we have a menthol product to test, we do a good job of minority recruitment.

It is possible for people to participate in more than one study. Because a lot of the folks are students, there's a lot of turnover, and so we don't often get that, but it's possible for it to occur.

DR. SAMET: Thank you. The question was largely just thinking about the generalizability of the findings.

Yes, Ellen?

DR. PETERS: Actually, I kind of have a related question. I'm curious if testing tends to be done in the context of the packaging because the packaging can provide a frame on the experience which actually influences the subjective ratings themselves.

DR. EISSENBERG: So in the acute test that we run, so those ones where we're looking at nicotine delivery in the laboratory, then the participant doesn't even see any packaging. In the week-long ones, Sarah, do you happen to remember? I think we take them out of the packaging and give them in a different container. Is that correct?

DR. EVANS: Yes. You usually blind your participants to the product that they're using. Correct.

DR. EISSENBERG: Well, I mean, it's not possible to completely blind them because it's

written on the -- but the package is often not shown to them.

DR. SAMET: Neal?

DR. BENOWITZ: It's also a question for Tom. In our smokeless tobacco studies, we found huge individual variation in nicotine exposure on the same exact dose. We gave people the same dose, 2.5 grams. And I think it's because of differences in either the saliva production, saliva pH, how much they swallow versus how much is bucco (ph). And I'm curious how much between-subject variation you see in nicotine delivery from these dissolvable products.

DR. EISSENBERG: Well, strangely, you'll think, that's not a question I often look at because it's a within-subject design. And so I'm always comparing someone to themselves under a different condition. But editors, for reasons that have never been clear to me, often require error bars, which are between-subject measures. And so you could look at the paper -- I don't know if we have that PDF -- and you can see the variability there.

I don't have a good recollection of the raw

data to tell you whether there's a lot of variability across subjects. What I can tell you is that in products like Ariva, Marlboro snus, the nicotine delivery is so low that the variability is cut off by the zero point.

DR. BENOWITZ: Just in general, I think that's an important -- variability is important because we're interested in vulnerable populations and subpopulations. And so we really would look to know what the extremes of exposure are.

DR. EISSENBERG: Can I just address that?

For Ariva, at least, the best study to look at that would be the one where we gave 1, 2, and 3, because in that 3-Ariva condition, there was much greater variability than in our normal, where we're just giving one at a time.

DR. SAMET: Bob?

DR. BALSTER: I'm pretty sure data don't exist on this, but these products could be used differently, by either swallowing them prematurely or placing them in different areas of the mouth.

I'm assuming you just don't have any

information about whether the subjects in these studies are putting the products where they are intended to be put or where they're recommended to be put and/or under various topographies of actual mouth placement or swallowing, how all that would affect nicotine exposure or, for that matter, toxicant exposure.

DR. EISSENBERG: Sounds like a great grant idea. We can parametrically manipulate the topography of use, but we haven't done that.

DR. SAMET: Well, if your general point is that we're going from fairly artificial systems, experimental systems, to what's going on in the real world, which we don't quite understand, I think that's an important issue for us in interpreting the studies as they are. And clearly there are issues in generalizability.

Other questions about the peer-reviewed literature? We've seen these studies. They were given to us in July. Do you have a question about your own study?

DR. HATSUKAMI: Yes, I do. I want to ask

myself a few questions.

[Laughter.]

DR. HATSUKAMI: No. Actually, I think what strikes me is -- and this pertains to generalizability -- is the consistency of results across the various studies, including mine and Tom's. And what's really apparent to me is that the abuse liability of products like Stonewall and Ariva are really quite low compared to their usual brand or products that have higher levels of nicotine.

So, now, that could be a good thing. But also it could be a negative thing in that, based upon the review of the literature, it appears that very few people would use these products alone because they may not lead to sufficient suppression of withdrawal, or it doesn't bring a lot of satisfaction, and so on. So I think that there's evidence to support that there's going to be a lot of dual use as a result of that.

The other point I wanted to make is that I think it's important to consider regional differences even though we see some consistency in patterns

because in our study we did conduct research in Oregon as well as Minnesota, and there were a few differences, regional differences, in terms of how people respond to the product. So in future studies, it would be important to do it at more than one site.

DR. SAMET: Bruce?

DR. SIMONS-MORTON: Just asking you guys who have experience with studies where users have tried these products, I think with initiation of smoking, for a lot of smokers, there's years of trial before they become regular smokers. I mean, there's a lot of variability in this pattern, but most regular smokers were occasional. And part of that is that there are negative effects from smoking. I don't know about the smokeless tobacco literature.

But I'm just wondering if these short-term effects are really just a matter of getting used to the product, and what your thoughts are about that.

DR. EISSENBERG: I have to think about that for a minute. I think, looking at the smoking literature as I've done for a different project, there are different trajectories of use. So it's not

always clear that it takes years of trying to become a smoker.

When it comes to the use of these products, I think what we heard yesterday about snus was that for some people, it was over a period of months that they became a snus user. And so in that context I think, to the extent that that's an accurate reflection of what happened, then I guess I would agree it would take a while for a smoker to transition to these products if they were going to.

I think the big difference here that we have to keep in mind is the nicotine delivery, for instance, of snus relative to these products and the withdrawal suppression of snus relative to these products.

What we're seeing in the lab is a product that doesn't deliver nicotine, that doesn't suppress withdrawal, and that isn't rated as highly acceptable to a smoker. And that combination of all three in other products that we've tested -- that is, products that produce smoke that are intended for smokers -- when you see that combination of low

nicotine, low withdrawal suppression, and low acceptability, you see minimal use or supplemental use with cigarettes and not eventual transition to the new product.

So in that sense, I think the lab studies are highly predictive of what we're going to see when it comes to dissolvable products.

DR. SAMET: Mark? Arnold?

DR. CLANTON: Nothing here.

MR. HAMM: No questions here.

DR. SAMET: Thanks.

If there's nothing else, I think we're going to make a change in the schedule, and I think we're going to continue with the RTI presentations that were scheduled for after the open public hearing since we're a little bit ahead of ourselves.

So I think what we're going to do is before our break at 3:00, we'll move on and have those presentations, I guess. And Jeanette, you're going to give us the overview. Thanks.

Presentation – Jeanette Renaud

DR. RENAUD: Yes. I'm going to provide an

overview of the documents that were received by the industry to FDA's Center for Tobacco Products.

As part of a contract with FDA's Center for Tobacco Products, RTI reviewed confidential documents related to dissolvable tobacco products submitted by the tobacco industry. In accordance with Section 904(b) of the Tobacco Control Act, FDA requested that tobacco companies submit documents related to seven topics for dissolvable tobacco products.

In particular, a letter was sent to 130 tobacco manufacturers in June of 2011, requesting that they submit documents within three months. And this information was intended to inform recommendations of the TPSAC regarding the use and impact of dissolvable tobacco products on public health.

Tobacco companies were asked to submit all documents and underlying scientific information related to research and research findings on dissolvable tobacco products for seven topics. And those included three marketing topics -- marketing

research, marketing practices, marketing effectiveness -- as well as health effects, toxicological effects, behavioral effects, and physiologic effects.

Eight tobacco companies submitted approximately 3300 documents, and there were about 65,000 pages across those 3300 documents. So documents could range in pages from one to thousands of pages. The number of documents submitted by a particular company ranged from 1 to about 2200.

The documents ranged in date from 1921 to 2011. Sixty percent were from 1999 to 2011, and about 75 percent, 74 percent, were between 1980 and 2011; so about 25 percent were prior to 1980.

With regard to the types of documents received, we received -- or FDA received -- 150 general reports; laboratory research, about 400; scientific reports, about 620; marketing research and marketing reports, about 180, 170; and 270 studies.

From those documents, those seven topics, there's going to be four presentations, brief presentations, today. I'm going to talk about the

behavioral effects topic; Dr. Brian Southwell will talk about the three marketing topics, the marketing research, practices, and effectiveness; Dr. Linda Brown will talk about health effects; and Dr. Brian Thomas will talk about toxicologic and physiologic effects.

For the behavioral effects, RTI identified, reviewed, and summarized industry documents related to behavioral effects of dissolvable tobacco products. Again, this information was intended to inform recommendations of TPSAC regarding the use and impact of dissolvable tobacco products on public health.

Although the work reported was done under contract with the Center for Tobacco Products at FDA, the content and conclusions of the presentations are those of RTI International. Again, we were looking at the behavioral effects of dissolvable tobacco products, and in particular, we were looking for information regarding initiation, dual use, switching, and cessation of tobacco.

Three reviewers examined about 287 documents

that were submitted by the eight tobacco companies. Sixty-three of those documents were self-identified by a few of the tobacco companies as relevant to behavioral effects. An additional 224 potentially relevant documents were identified through keyword searches using search terms like "initiate," "initiation," "dual use," "switched" and forms of switched, "migrate," "migration," "cessation" or "quit," "abstain" and "abstinence."

Data reported in the open meeting, this meeting, are limited to information deemed not commercial confidential. The commercial confidential information was presented to TPSAC subject group experts in closed session.

But in regard to that information that was summarized, many of the documents are proposals, protocols, IRB proposals, and therefore don't always include a lot of findings, research findings. And as well, they were short-term clinical trials for test products and concepts.

DR. SAMET: Maybe we should just probably keep moving.

Presentation – Brian Southwell

DR. SOUTHWELL: Good afternoon. My name is Brian Southwell. I'm going to spend a few minutes talking about what we found with regards to marketing research and marketing practices in our review. I am going to offer the similar disclaimer as Jeanette did, that the work that we did was under contract for the FDA, but the conclusions that we've reached and the information I'll present are those of RTI International alone. In this particular brief presentation, I do want to offer just a summary of what we found and some brief interpretation of those findings.

With regards to marketing research and marketing practices, we had a team of four coders total taking a look at those documents. I'll describe the scope of the documents that we looked at in just a moment. Those on the review team included not only me but also Suzanne Dolina, Carrie Lawson, and Cindy Soloe, all employees at RTI International.

We looked at a total of 261 documents. The majority of these were self-identified by industry.

We also did a supplemental search to uncover additional documents that may well have been relevant to marketing research or marketing practice. Those were included in our review as well.

Again, I need to stress that there will be some data that are reported here in the open meeting, but that's limited to information that's been deemed not commercial confidential. The commercial confidential information was presented earlier, yesterday in closed session.

With regards to marketing research and marketing practice, the documents ranged largely in the last decade or so, from 1999 through 2011. Most of the documents that we looked at were research or planning reports and memos. Some of the documents were of a different nature, were actually raw data sets themselves or were simply copies of packaging.

Generally, I'll offer just a brief overview of our thematic points of emphasis that we found. There was in many instances a discussion of the extent to which dissolvable tobacco might be framed as an impulse purchase. We see this in evidence in a

couple of ways, an emphasis on point of sale marketing in addition to other avenues of promotion of dissolvable tobacco; relatively little emphasis on longer-term considerations with regards to, for example, health consequences.

There is some effort to present the products as an accessory item for current smokers. And certainly there's a range of current tobacco users that are the potential target market for this. We're not only talking about cigarette smokers but certainly, at the very least, those who are using chew or moist smokeless tobacco are in the potential audience for dissolvable products as well. There's been some effort to position these products, perhaps unsurprisingly, as relatively new and novel and as something different than those that have been offered in the past.

We took a brief look at the sum total of those 261 documents and categorized them with regards to various points of emphasis. I have an array of categories listed here. In no one case are we necessarily suggesting that a particular

interpretation or viewpoint was predominant with regards to a category, simply that that category or idea or notion was referred to in the documents in question.

So you can see here, for example, many of the documents talked about, in some way, audience characteristics or general reference. There was general reference to cigarette smoking. And there are relatively lower numbers for some of the other categories.

I want to briefly point out just a couple of observations about the points of emphasis. While many of the documents did in fact refer to cigarette smoking, there was relatively little direct and explicit reference to smoking cessation. Less than a quarter of the documents explicitly referred to cessation in any way, and a reference could be anything from a mention in a report or a memo in an interpretive way to a direct quote from a formative research participant; and regardless, taking that broad view, less than a quarter of the documents actually referred to smoking cessation.

In terms of the balance of product benefits and costs, these are marketing reports, and so it perhaps is unsurprising that you see a relative emphasis on product benefits. More than half of the documents in some way described some of the potential perceived benefits to use of the product. We'll talk a little bit about what some of those were in just a moment. Relatively less than half of the documents actually talked about product costs from the perception of consumers.

Last, just to emphasize the earlier point that we're not simply talking about current cigarette smokers, fully more than half of the documents talked about other tobacco products, whether it be snus or moist smokeless tobacco. So, many of these documents are not just talking about dissolvable tobacco or cigarette smoking.

In terms of what we found across and as a composite view -- and these, remember, are documents submitted by a number of different companies and organizations -- by and large, we actually saw in this group relatively little explicit attention to

simple channel selection; so relatively less emphasis in this particular set of documents with regards to magazine advertising, for example, as a strategy.

My of the attention was -- and actually, there's relatively little attention on audience demographics, per se. There'll be some brief general reference to adult smokers, for example, and maybe an age bracket, but relatively less emphasis. There's probably more emphasis on psychological factors that characterize potential users than on demographic ones.

Again, just to emphasize this point, not only in terms of the counts but I think also qualitatively, we saw much discussion about the possibility of recruitment of current moist smokeless tobacco users as potential users for these new dissolvable products. So that was part of the strategic discussion as well in many of the places that we looked at.

There's relatively little discussion in these documents with regards to the notion of dissolvables purely as a smoking cessation aid. Much of the

discussion, much of the reference or emphasis on dissolvable products with regards to other types of products is on this notion that perhaps there's a temporary curbing of craving that it's possible to promote or at least to discuss as a benefit.

It also seems to be the case that there's much emphasis and discussion of the extent to which tobacco product use in general is about more than nicotine delivery. There's an emphasis in the documents that we looked at on the importance, for example, of hand-to-mouth activity. And you've seen this with regard to the array of different dissolvable products. Some of those dissolvable products allow for and use more hand to mouth activity or permit more hand to mouth activity than others.

In addition, there were other perceived benefits amongst respondent in various of these studies. One that was emergent as a general theme was the notion that these products are useful in terms of impression management, particularly in places where there's social sanction against or

outright ban on smoking, and also, the potential convenience offered by these products was a point of emphasis in many places.

So just to briefly summarize, then, our view of marketing efforts as they are presented in these 261 documents suggest that there is, by and large, an emphasis in recent years to promote dissolvable tobacco products as a potential impulse buy and as something that is available and promoted through point of sale means.

There's an emphasis on emotion in many of the advertising strategies that are employed, a focus on relatively immediate positive consequences that are offered, and relatively little focus on long-term costs.

There's a presentation of dissolvables as an accessory item explicitly in at least some of the advertising efforts to date, and there is an acknowledgment, a recognition, that dissolvable products are not monolithic, that they offer an array of choices. There are different products that could perhaps be positioned or targeted for different

groups and different audiences.

Thank you very much.

DR. SAMET: Thank you.

Presentation – Linda Brown

DR. BROWN: So I'm going to be providing a review of the industry documents related to the topic of health effects. Just sort of as a background from this, I don't think health effects was probably a primary focus of most of these documents. So it was something that we had to kind of go in and search for. So I think, as we've seen in other things, it's probably an area that does need more work.

So again, the purpose of this is to inform recommendations of TPSAC regarding the health effects of dissolvable tobacco products and by identifying the industry documents of potential interest in this area. And again, although this work was done under contract with FDA's Center for Tobacco Products, the content and conclusions for this presentation are those of RTI.

So under the topic of health effects, we looked for information regarding health warnings.

Short-term health effects included reported adverse events, injury, and those results were considered commercially related and were reported in the closed session yesterday; and accidental ingestion and child safety concerns.

First I want to set the stage for this health effects presentation by reviewing some of the background related to the safety of smokeless tobacco, including dissolvable tobacco products.

According to the National Cancer Institute and the International Agency for Research on Cancer, there's no safe form of tobacco, and at least 28 chemicals in smokeless tobacco have been found to cause cancer.

According to NCI, the most harmful chemicals are tobacco-specific nitrosamines, TSNAs, which vary by tobacco product. They are formed during the growing, curing, fermenting, and aging of tobacco. Scientists have found that the risk of cancer is directly related to the level of TSNAs.

According to NCI, IARC, and the Centers for Disease Control and Prevention, there are a number of

diseases linked to the use of smokeless tobacco. These include cancer, specifically of the oral cavity, esophagus, and pancreas; oral health, including oral lesions such as leukoplakia, gum recession, gum disease, and tooth decay; reproductive health concerns such as preeclampsia, premature birth, low birth weight, and reduced sperm quantity and quality; and nicotine addiction and dependence.

It's also important to understand that no epidemiologic studies have been performed with dissolvable tobacco products, and that the long-term effects are unknown because of the relatively short time these products have been widely on the market.

Two epidemiologists on the RTI team reviewed the industry documents for relevant information on the health effects of dissolvable tobacco products. We reviewed the documents using three methods. One, we used company designation of health effects; two, we used search terms "health" and "injury," and three, we reviewed document summaries.

Of the 369 documents and 20,911 pages we reviewed, we determined that 68 documents contained

relevant information, 280 did not contain relevant information, and 21 were either duplicate documents or had duplicate content.

This slide illustrates the total number of each type of document reviewed, blue bars, and the subset of each type that we considered relevant, the yellow bars. For example, we reviewed the most documents in the Study Report, 79 items, and Toxicologic Report, 108 items, categories. However, the percentage of relevant documents was highest for the FDA Documents, 100 percent, and Other Study-Related Documents, which we call OSRD, categories, and there were 77 percent in that.

A listing of the subtypes of documents within each category is included in the next several slides. Within the Memo category, we included emails as well as memos related to basic science, laboratory research, product evaluation, and scientific reports, as well as memos from the human research review committee and the product assessment division.

The Protocol category is comprised of clinical study and scientific protocols. We grouped

clinical and laboratory reports and manuscripts under the Study Report category. Included in the Other Study-Related Documents group are confidentiality statements, exit interview forms, informed consent documents, opinion surveys, product brochures, study proposals, and study tables.

We grouped hazard management reports, hazardous substance data bank reports, product hazard analyses, and risk assessments under the Hazard Report category.

As I mentioned previously, the category with the most reviewed documents is Toxicologic Reports, including commercial product lists, FEMA assessments, ingredient lists, material safety data sheets, and vendor food documentation. We identified these documents while searching under the keywords "health" and "injury," however, none of them included information relevant to health effects.

We grouped reports and articles describing the frequency and outcomes of accidental ingestion of tobacco products in children, the hazardous potential tobacco product ingredients, and nicotine poisoning

in children under the Literature Review category. Included in the Presentation category are exit interview results, laboratory research, poster abstracts, scientific reports, and study design and objectives.

The final types of documents we reviewed were copies of documents provided to FDA and those we classified as Other. The FDA documents included correspondence, modified risk tobacco product applications, and submissions pursuant to the Family Smoking Prevention and Tobacco Control Act.

Under the Other category, we included article request forms, market surveys, monographs, notes, pages from the Canadian Center for Occupational Health and Safety and from the Encyclopedia of Occupational Health and Safety, publication reviews, search requests, summary of commercial requests, and tobacco product/process change in management forms.

According to the information reviewed, the tobacco companies are complying with the Family Smoking Prevention and Tobacco Control Act that requires every smokeless tobacco package and

advertisement to include one of the following four mandated warnings:

One, "Warning: This product can cause mouth cancer"; two, "Warning: This product can cause gum disease and tooth loss"; three, "Warning: This product is not a safe alternative to cigarettes"; and four, "Warning: Smokeless tobacco is addictive."

This slide shows an example of three of the four health warnings that appear on packages of Camel sticks, orbs, and strips.

We identified short-term health effects by reviewing lists and tables of product-specific adverse events included in study reports and presentations. In general, the tobacco companies felt that most of the adverse events reported were associated with oral absorption of nicotine. Regarding adverse health effects from use of Ariva and Stonewall, the company reported receiving reports of burning sensation, hiccups, and nausea, primarily from smokers using smokeless tobacco products for the first time.

Further, in applications to the FDA, the

company noted that Ariva BDL, Stonewall BDL, original Ariva, and original Stonewall are nauseating to the non-tolerant users. Ariva BDL and Stonewall BDL are newer dissolvable tobacco products similar to original Ariva and Stonewall in nicotine content, but with levels of TSNAs that are below detectable limits by most current standards of measure.

A study by Carpenter and Gray in 2010 reported that the most common adverse events among smokers who used Ariva along with conventional cigarettes were nausea, hiccups, and insomnia. Further, the product label on a picture of Ariva states, "As with other tobacco products, some users may experience temporary dizziness, heartburn, or nausea."

The following short-term health effects were reported as adverse events in company studies for various dissolvable tobacco products: indigestion, heartburn, or upset stomach; nausea or vomiting; increased burping; throat discomfort, burn, or irritation; coughing; mouth tingle, burn, or irritation; tongue irritation; gum or cheek numbness,

burn, or irritation; tooth or gum sensitivity; dizziness; nervousness; excess saliva; dry mouth; headache; increased heart rate; and hiccups.

Concerns have recently been raised about smokeless tobacco products and acute toxicity, especially from nicotine associated with accidental ingestion by young children. According to 27 years of American Association of Poison Control Centers, AAPCC, annual reports from 1983 to 2009, 0.37 percent of exposure contacts involved tobacco products, the majority of which 89 percent occurred in children less than six years of age. In addition, from 2005 to 2009, there were 5,250 reports of children ingesting the subcategory of tobacco products, chewing tobacco, or snuff, resulting in eight major outcomes but no fatalities.

A literature search and review were conducted related to accidental ingestion of tobacco products among children. According to surveillance data from the National Electronic Injury Surveillance System, NEISS, cited from an article by Franklin and Rogers published in 2008, the estimate of nonfatal poisoning

rates for children less than five years of age treated in U.S. hospital emergency departments in 2004 was only 0.7 percent for ingestion of tobacco products, compared with 59.5 percent for ingestion of oral prescription and nonprescription drugs.

In 10 years of marketing Ariva and Stonewall, the company never received a report of serious pediatric toxicity requiring medical evaluation or treatment. The few reports they did receive involved toddlers who obtained the product from a third party source.

The company conducted a review of the entire AAPCC database for 2009 through the first quarter of 2010. This review revealed 527 pediatric snuff cases, where product could be identified. Of the 527 cases, 524 involved a moist snuff product, one involved Ariva, one involved Stonewall, and one involved an unidentified dissolvable tobacco product. All three pediatric cases experienced either no effect or a minor effect and resolved with home care. According to the company, this recent AAPCC experience does not indicate a significant pediatric

risk from Ariva and Stonewall.

In one of their documents, the company stated that they have done very limited child safety testing for Ariva and Stonewall. However, based on the very few reports of pediatric accidental report -- less than a dozen in nine years -- and the product complaints from adults that the package is hard for older adults to open, they feel confident that the packaging is adequate to deter young children.

According to the company, symptomatic ingestions of Ariva and Stonewall are possible, but serious toxicity is unlikely. No cases of serious toxicity, pediatric overdose, hospitalization, injury, or death involving Ariva or Stonewall have been reported to the company.

No specific information on accidental poisoning was available for Marlboro and Skoal smokeless tobacco sticks. However, according to documents provided by the companies, the incidence and severity of accidental poisoning is very low for smokeless tobacco products, and they do not expect results to be different for these products.

This slide is just a listing of the references that I cited in my presentation. Thank you.

DR. SAMET: Thank you. I guess we have one more presentation?

DR. BROWN: Yes.

Presentation – Brian Thomas

DR. THOMAS: So I'm Brian Thomas, and my topics that I reviewed were on the toxicological and the physiological effects of these dissolvable tobacco products. And the same disclaimers and same purpose for the presentation.

The two topics, again, were toxicological effects and physiological effects. And many of the documents were coded with both terms, "toxicological" and "physiological," so they were contained within the same set of documents.

I had 2,730 documents to be reviewed by my team that were submitted to the FDA's Center for Tobacco Products by the tobacco companies that were stated to be relevant to the two topic areas. And each document was reviewed by one researcher and

initial screen to eliminate documents of little or no scientific value. And then those documents that were found to contain value were reviewed by at least one additional reviewer, including myself, and the most significant information was compiled for further review and presentation. We also did additional keyword searches across all the submitted documents, as necessary.

Unfortunately, all of the content that I reviewed was deemed commercially confidential by the FDA, and I cannot present it to you today.

[Laughter.]

DR. SAMET: Well, I'm glad you had the disclaimer.

[Laughter.]

Committee Discussion

DR. SAMET: So why don't we open up for any discussion or clarification. And actually, maybe it has to do with what we have, but actually, I wanted to check.

Linda, you made a comment that said the company has done very limited child safety testing.

DR. BROWN: That's what they said, too.

DR. SAMET: Okay. So that was my question, is that you found few reports or they actually said they had done little testing. There's a difference.

DR. BROWN: They specifically said --

DR. SAMET: I'm sorry. Why don't come to the microphone. Sorry.

DR. BROWN: Yes. That was a quote from one of the documents. And it may have been from one of the FDA documents where they actually had extensive review when they had submitted some documents to FDA about their products for some kind of -- I think before when they were trying to get some kind of approvals or something like that. So that might have been in something like that.

DR. SAMET: Thank you. Just looking for clarity on that point.

Other questions or comments about what we just heard? Yes, Sherry?

DR. EMERY: I have a question for Dr. Southwell. The striking thing to me about what you presented with the marketing information was

really what wasn't there. And it made me think that since the industry is so very good at promoting their products and advertising, that there must be more research. And I would hypothesize it's done at the advertising agency or someplace.

Now, that wasn't part of what was submitted in this request, clearly. But is it possible to get that, or is that outside the scope of what we would have access to?

DR. SOUTHWELL: I think that question's probably outside my scope of being able to answer.

DR. EMERY: Yes. But I mean, would you -- just given what you know, do you think that there's probably more out there?

DR. SOUTHWELL: I really can't speculate on that, unfortunately, or for better or worse.

DR. EMERY: Is it possible to get other information about their marketing studies?

DR. EVANS: We had asked for specific information in the 904(b) letter, and that's what they turned in to us. So it was sort of a broad overview. It wasn't very -- it was actually

mentioned in one of her slides, slide 4. We asked for marketing research, marketing practices, and marketing effectiveness. And based on that, what we asked for, that's what they turned in, that RTI analyzed.

DR. EMERY: Okay. Thanks.

DR. SAMET: Neal?

DR. BENOWITZ: I'm just curious. Did you look to see how many documents were available on public document archives of the ones that were submitted?

DR. SOUTHWELL: That's a good question. In our particular category, and I think in some of the other categories of documents, there were publicly available articles, for example, that were as part of that. In our particular group, I think relatively little of these would be available publicly. These seem to be internal documents.

DR. BENOWITZ: I raise that because for the menthol report, it was useful that there were some academic centers that analyzed and published the document information. And if these documents were

available, that would be something that would be useful, I think, to be done, so that there's public understanding of --

DR. SOUTHWELL: Certainly there has been some work to take a look at patterns in advertising, for example, obviously that are publicly available. And that's starting to emerge, I think, in various academic centers as these -- as there's a track record and availability of that content.

Insofar as intent can be gleaned from that, and certainly a description of various strategies that are used and employed in magazine ads, for example, that's something that the people are starting to track.

DR. SAMET: Ellen?

DR. PETERS: This is a follow up to what Dr. Emery was saying. There's sort of a strange lack of perceived benefit for this product that's documented, in my opinion. The public literature could possibly underestimate the perceived benefit of the product due to the packaging's not there before they've experienced the product, possibly. And this

is -- I'm speculating on this. The decision context isn't there. So the context in which they might experience the product can also influence the experience of that product.

It could be, based on what you're saying just a little bit ago, that maybe there are some other questions that could be asked if all of those perceived benefits are really short-term, like, I just want to curb my craving temporarily. And there are some other short-term benefits that were mentioned.

But even in the industry documents that you reviewed, and maybe I missed it, but the benefits appear to be short-term, that focus on dissolvables curbing craving temporarily, the hand to mouth activity. But based on what you've seen, do consumers like these products? How do they feel about the products?

DR. SOUTHWELL: I think it probably would be a slight mischaracterization to frame everything in terms of absolute short-term and immediate benefit when you consider, for example, something like the

value of human relationships and the possibilities that these products offer for impression management, for not being the person who's violating the smoking banner, who's irritating others around them that don't like smoke.

So I think that's certainly a major benefit that's been discussed. So I think the ongoing social nature of both product use and those relationships is certainly a point of emphasis in these documents, and I certainly think you see that reflected in some of the marketing approaches.

So just a slight departure from what you said, and I probably didn't do sufficient justice to that particular idea in this presentation. So thanks for pointing that out.

DR. PETERS: But do products seem to -- do consumers seem to like the products, based on the industry documents?

DR. SOUTHWELL: That's a very difficult question to answer in the abstract. There's certainly plenty of evidence. There seemed to be sufficient evidence of market demand and desire for

the products, that some of the early efforts and early formative research has seen its way through to actual product sale and to strategy.

So I think that there is certainly quite a bit of affirmative evidence that there was interest in these products, I guess if that's -- absolute liking is sort of a difficult concept. But I think in terms of agreement that particular advertising messages were worthwhile, the notion that the perceived benefits were ones that were of value, I think there's clear evidence of that in the documents that we reviewed, anyway.

DR. SAMET: Tim?

DR. MCAFEE: Yes. Thank you very much. I just essentially wanted to confirm an impression that I'm developing based on what you had said that is again helping to resolve what I think some of us are perceiving as a bit of a mystery around the niche that the dissolvable products, as currently constituted, are trying to fill.

Part of the mystery to me is why the relatively low amounts of nicotine for most of them,

to the point at which they're not being very effective at full-bore urge control. And I think that's part of it, that we're coming at this from the perspective of thinking of it.

Well, if there were a public health benefit niche for these, it would be taking current smokers and migrating them to use of these products as a replacement for cigarettes, and that clearly, what I'm gathering from what you got from the documents is that there is an explanation for this, and that that's not what they're -- that is not the niche that they're designed for, being marketed for, et cetera. But this is more around impression management, which I would view as a euphemism for how to be able to keep smoking despite secondhand smoke restrictions and cultural shifts, but that they're not -- at least, you're not finding evidence that they're being designed literally as potential replacement products, which would explain why they might have lower nicotine levels.

Does that sound right?

DR. SOUTHWELL: Certainly across the 260

documents that we reviewed, and particularly those that we reviewed within the last five years, there's very little discussion of cessation explicitly. And when the discussion does arise, it's amongst research participants, and it's not always a positive or affirmative mention; that often there'll be a notion that perhaps this isn't something that would be a replacement, in fact. So yes, I think that's fair.

DR. SAMET: Dan?

DR. HECK: Yes. I think, to this question from Dr. Emery and Dr. Peters and others regarding the relative simplicity of the marketing document summaries that have been presented, I think we should remember that under the current regulated regime, the companies are explicitly severely constrained in their ability to communicate to consumers information about relative risk or relative exposure, and also, explicit information or advice about use in cessation. So, in the present condition, the marketing is essentially limited to presenting the product to existing tobacco users and trying to encourage trial and acceptance of the product.

So perhaps as we proceed forward in these other areas, with modified risk and the potential, if there is some, for cessation use -- which has been of, you know, high interest in the academic research, but it's not surprising to me that this doesn't find its way in the marketing interest currently.

DR. SAMET: Tim?

DR. MCAFEE: Just a quick follow-up. I think that's a very important point, and I'm just curious. Whether the tobacco companies would feel constrained from marketing them as replacement products as opposed to bridge products, I'm not sure there would be anything -- you couldn't make a product claim around cessation in the sense that this was a cessation aide. But is there really anything that would keep a tobacco company from marketing it?

I actually kind of remember something from an earlier presentation where R.J. Reynolds actually did one of its events that actually did seem a little along that line, where they were doing the -- you'd get a prize if you switched completely for 30 days or 3 months or something like this.

What's the real constraint on pushing it as a true substitute, as opposed to an augmenter?

DR. SAMET: I'm not sure that's a Dan question, in fact.

David, were you going to -- did you have a question or comment on this? I don't know, Dan, if you want to respond.

DR. HECK: Well, I don't know the exact chronology of that. Certainly I think early on in the era prior to FDA regulatory oversight, it's possible that some of those older campaigns may have touched a little closer to the cessation or even implying or communicating reduced risk.

We did hear in the Swedish situation that the Swedish population is generally quite better informed, I think, of the relative exposures for the traditional product there versus smoking. And I think we can maybe look forward to the day when the U.S. consumers are similarly well-informed about the relative exposures and risks for the different products.

DR. SAMET: Tom?

DR. EISSENBERG: Well, actually, I just want to follow exactly on what was just said. I was struck yesterday by the Swedish experience, that -- and again, if I remember correctly, the transition from smoking to the high-nicotine, high-withdrawal suppression snus products occurred in the absence of marketing by the Swedish Match and the Swedish snus producers. And so its not clear to me marketing is what's required. It seems that it's more clear that what's required is the higher nicotine, higher withdrawal suppression.

DR. SAMET: Let me ask, Mark, Arnold, do you have any questions? Comments?

DR. CLANTON: No questions.

MR. HAMM: No questions here, either.

DR. SAMET: Thank you.

Other questions for our panel?

[No response.]

DR. SAMET: Thank you, then.

I think what we'll do is we will break until 3:00 and then begin the open public hearing; and just a reminder not to discuss things during break.

(Whereupon, a brief recess was taken.)

Open Public Hearing

DR. SAMET: We're going to go ahead and get started again with the open public hearing portion of this meeting. I'm going to read a statement.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning

of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Caryn is going to give the speakers instructions on how the timing will work.

MS. COHEN: We have a very full session today. And as all the speakers know, you're going to have three minutes. After two minutes, when you have

one minute left, the yellow light will go on and you will hear one beep. When your time is up, the red light will go on, you'll hear two beeps, and your microphone will be turned off. So just preparing everybody.

DR. SAMET: And we'll invite the committee after each presentation to see if there are questions or comments. That is in addition to the three minutes. I guess we have speakers that are in some sort of random order. They know their order. Right.

Our first speaker is Andrew Wolford. Please go ahead.

MR. WOLFORD: I started smoking at the age of 14 as a freshman in high school. What started as a social activity quickly turned to something that would control my life for nearly 21 years.

During those 21 years, I chose to attempt quitting multiple times, and unfortunately, multiple times I failed. I tried to quit cold turkey. That lasted about a day, maybe a day and a half. I used nicotine gums, lozenges, patches, snus, even hypnotherapy. All of them had their different levels

of success, but nothing ever lasted long-term. The desire to quit smoking was there. However, the physical needs as well as the habitual needs were just too strong for me to break.

The multiple attempts spanned the course of those 21 years. The longest period I was smoke-free was maybe three or four months. They were a continuous struggle, and my life seemed easier as a smoker. It was less hassle, for lack of a better term.

I've now been smoke-free for over 10 months because of electronic cigarettes. I chose to use that as my form of reduced risk for my nicotine intake. Since I've stopped smoking, I breathe easier. I snore less at night. I sleep better. My blood pressure has dropped. I've never felt better in my life.

Now, while a chose electronic cigarettes, I firmly believe that any alternative source for reduced risk for nicotine intake is a better method than combusted tobacco for anybody who wants to continue their use of nicotine or can't do without.

For smokers who find quitting nicotine altogether too hard, I feel we should not limit the amount of alternative methods for replacing how we get our nicotine. Dissolvable tobacco products are affordable and are helping to keep many smokers off cigarettes.

I feel the FDA needs to make sure that these products are other alternative methods for nicotine intake are kept available as an alternative for nicotine intake.

DR. SAMET: Thank you.

Questions or comments from the committee? Patricia?

DR. HENDERSON: Have you used any dissolvable products for --

MR. WOLFORD: I did. I used snus. It just wasn't for me. I didn't like the flavorings, is more what it was. And I don't like the smell of smoke now. I've never wanted to go back after that. And that was the main quit. I don't mind nicotine. I enjoy the nicotine feeling. It's relaxing. But I find the e-cigarette provides more of a habitual need

for me than all the other methods that I tried.

But I did try snus, and it just -- it wasn't for me. But I had no problems with it.

DR. SAMET: Thank you. And Mark and Arnold, I'll just ask, if you want to comment, just speak up and we'll get you in.

Thank you, Mr. Wolford.

MR. WOLFORD: Thank you.

DR. SAMET: Next, Gregory Conley.

MR. CONLEY: Hi. My name is Gregory Conley. I recently graduated from Rutgers University in New Jersey with a JD MBA, and I have been smoke-free thanks to electronic cigarettes, Swedish snus, and recently, dissolvable tobacco of various sorts, including Skoal sticks and the Camel dissolvables as well as Ariva, since August 10th of 2010.

I am here to strongly urge you to look honestly and intelligently at the dissolvable tobacco issue and notice and note that this product, there is no evidence before you that suggests that it is not, like Swedish snus, 98 to 99 percent less harmful than smoking. And there are a couple points that I would

like to make.

The first is that please remember that under Judge Leon's ruling about e-cigarettes, which was upheld by the D.C. Circuit Court of Appeals, GSK tomorrow is free to take its dissolvable lozenge and market it as a tobacco product. And they can say, use it as long as you wish.

So I want to encourage you, as Bill Godshall pointed out in his testimony, when you are writing your report, consider the fact if GSK decides to market its dissolvable lozenge for long-term use as a tobacco product, is the population health effects and the individual health effects going to be any different from Ariva, Camel, Skoal, and Marlboro products already available on the market?

Furthermore, I want to caution the panel not to cherry-pick its data. Some people that have given presentations before TPSAC -- today, yesterday, previous meetings -- seem to look for the worst data. And at all these meetings, I've never heard anyone bring up Bill Godshall's testimony.

For me, reading the various testimonies that

Godshall has submitted has been an educational experience. He puts a lot of time into those, and there's a lot of data in there that was not discussed, including the question that was brought up earlier today about off-label use of NRT.

If you actually look at some of his old testimony -- I believe including the testimony submitted for today's meeting -- you'll see that I believe it's something like 95 percent of NRT use is off-label because the minute you start using a cigarette, you are using NRT off-label because the label specifically says do not use this in conjunction with a tobacco product.

With 45 seconds left, my remaining point is, thankfully, there has not been much here today talking about this product as candy. But unfortunately, some of the groups who are represented by reps on the panel, they frequently go out to the media and they inaccurately describe this product as candy.

I want to encourage those groups not to do this. You are just asking for youth to see this

product as candy and to give you the data about poisonings that it seems that some people really want to happen.

So in conclusion, please, you have the data in front of you that shows dissolvable tobacco 98 to 99 percent less harmful. So please, use it, consider it, and write a legitimate report. Thank you.

DR. SAMET: Thank you.

Questions or comments for the speaker?

[No response.]

DR. SAMET: Thank you.

Next, Chris Proctor, affiliated with British American Tobacco.

DR. PROCTOR: Thank you. Good afternoon. I'm Chris Proctor. I'm the chief scientific officer for British American Tobacco.

I just wanted to share with you an experience that we've had trying to bring smokeless tobacco products to various markets, not in the U.S. but in other countries, and the kind of barriers that you might experience, or we've certainly found, in doing that.

To start out, I should say -- and I do recommend a report by the Royal College of Physicians that was published in 2007 which evaluates the health effects of smokeless tobacco, and clearly determines that snus use is substantially less harmful than cigarette smoking, and really quite a good report to have a look at.

Because of that, we've done quite a lot of science related to, particularly, snus. We looked at chemical characterization, toxicology studies, and we've done some consumption studies, all of which are either in the peer-reviewed literature or being submitted to the peer-reviewed literature.

Because of the potential of snus for tobacco harm reduction, we tried to see if smokers would substitute for cigarette smoking to snus in three countries, in Canada, in South Africa, and in Japan. What we found through those experiences were, there are considerable barriers for that substitution.

There are barriers in terms of the behavior that is involved in the product use. There are barriers in terms of just what taste and flavor comes

with the products. There are barriers in terms of male and female use, certainly with snus. And there's barriers in terms of understanding.

One of the challenges that we really faced in doing this was to try and get the regulatory and the scientific and public health community behind the initiative, to get smokers, obviously, to quit in the first place, but if they would not quit, to substitute to something which is substantially less risky. And those barriers we were unable to overcome in any of those three companies.

So simply as a sharing of information to that committee, that's what we found. Smokers aren't necessarily going to adopt these products. They are quite different in their form and in their taste. And that adoption will require a broad church of alliances, I think -- tobacco companies, yes, but also the regulator and the public health authorities -- to get behind those products, to have them as a proper substitution, and then hopefully get tobacco harm reduction.

Thank you.

DR. SAMET: Thank you.

Questions? Tom?

DR. EISSENBERG: Yes. I wonder if you can tell me what you make of the statement that we heard yesterday from Swedish Match that the transition for many Swedish smokers to complete snus use occurred in the absence of marketing, and it seemed like, therefore, in the absence of any governmental message.

DR. PROCTOR: I'm not sure it would be in the absence of a governmental message. Swedish snus is very well know in Sweden. I think some of the evolution from cigarettes to snus was cultural; either people were following what was a lower socioeconomic behavior deliberately because they wanted to support that, but also it's very well known in Sweden that snus is less harmful than cigarette smoking.

Where we tried to look at this, certainly in Canada -- Health Canada has statistics on this -- and in South Africa, we found that people assumed that snus was as dangerous or more risky than cigarette

smoking. So in the absence of that communication, which I think probably was there in Sweden, it's quite hard to get people to evolve.

DR. SAMET: Anyone -- Patricia?

DR. HENDERSON: Did any of your work in Canada or -- did you say Australia?

DR. PROCTOR: No, South Africa and Japan.

DR. HENDERSON: South Africa -- primarily in Canada revolve among aborigines?

DR. PROCTOR: Native Canadians? No. Well, we tried to work with Health Canada on how we would present this, but it was mainly through stores trying to get people to adopt in that way.

We did media. In fact, I turned up in Ottawa, the seat of government in Canada, to give press statements about what the potential for snus would be in tobacco harm reduction, but actually, no one turned up from the government and I presented to an empty press room.

So it was really very, very hard to get an engagement, possibly because, unlike in the U.S., there isn't that agency that's there to kind of

capture the feelings and there to express those to the public.

DR. SAMET: Neal?

DR. BENOWITZ: I assume from what you were saying that the goal of these was harm reduction, to reduce smoking, that was the goal of this --

DR. PROCTOR: Yes. We're assuming that for snus or any smokeless tobacco product to be harm-reduced, it has to be a complete substitution from cigarette smoking to that product.

DR. BENOWITZ: Can we get copies of reports or summaries of these studies?

DR. PROCTOR: Yes. There are quite a few of them on bat-science.com, on my website. We presented some at the Scientific Society for Research on Nicotine and Tobacco, and we're in the midst of reporting it. So where the data is of quality publication, we're publishing them. I'm very happy to send you in some data on that.

DR. BENOWITZ: Yes. Or I think the abstracts would be useful, too.

DR. PROCTOR: Yes. I can easily do that.

DR. SAMET: Ellen?

DR. PETERS: You mentioned that the perceived risks differ cross countries. What are the perceived benefits of these products? Why do people use them? And does that differ across countries, too?

DR. PROCTOR: Yes. We looked at South Africa where all tobacco really is very rarely used. And so if anything, there are negative connotations to them. The same would be true in Canada.

In Japan, the benefit would be a social one, very much so. The Japanese culture is very courteous, and so to switch from smoking to something which didn't involve smoke would be a culturally beneficial thing.

In persuading the benefits -- I mean, you can talk about the health risks, but without a public health support discussing the health risks, you can't do that in marketing or communication from a tobacco community. It has to be a broader church of communication that allows people to see the context of these products and what potential benefits they do have.

DR. SAMET: Okay. Thank you.

Next presenter is Bill Godshall from SmokeFree Pennsylvania.

MR. GODSHALL: Hi. I'm Bill Godshall, founder and executive director of SmokeFree Pennsylvania. Since 1990, we've advocated local, state, and federal policies to reduce indoor tobacco smoke pollution, reduce tobacco marketing to youth, increase cigarette tax rates. And in 2007 I convinced Senator Mike Enzi to amend the Tobacco Control Act to require picture warnings on all cigarette packs.

For disclosure, neither SmokeFree Pennsylvania nor I have ever received any funding from any tobacco, drug, or e-cigarette company, nor the FDA.

I urge TPSAC members to carefully review the hundred pages of written comments I submitted evaluating hundreds of studies and other evidence finding smoke-free tobacco products are about 99 percent less hazardous than cigarettes, and that several million smokers in the United States have

already quit smoking cigarettes by switching to smoke-free alternatives, which is more than have quit by switching in Sweden.

Since more than 99 percent of all tobacco-attributable deaths in the United States are caused by tobacco smoke, it is vitally important that TPSAC's report on dissolvables acknowledge the exponential differences of risk between cigarettes and smoke-free tobacco products.

Smokers have a human right to be truthfully informed that smoke-free products are far less hazardous alternatives to cigarettes. Consistently, health agencies have an ethical duty to truthfully inform smokers that smoke-free alternatives are far less hazardous than cigarettes.

Since several million smokers in the U.S. have already switched to smoke-free tobacco alternatives, it's mathematically impossible for smoke-free tobacco products to increase tobacco-attributable mortality, even if every American begins using dissolvables or other smoke-free products.

Dissolvable products are target-marketed to

smokers as alternatives to cigarettes. Most new users of smoke-free products are adult smokers, and smoke-free products pose no risk to nonsmokers. On a scale of mortality risk from 1 to 100, where NRT products are a 1 and cigarettes are 100, all smoke-free tobacco products sold in the U.S. and Sweden appear to be below 2.

Smoke-free tobacco products and NRT products have very similar health/safety risk/benefit profiles. Unfortunately, the FDA has falsely stated to date, "No tobacco products have been scientifically proven to reduce risk of tobacco-related diseases, improve safety, or cause less harm than other tobacco products." That's a lie.

In 2009, the FDA misrepresented its own lab test findings on e-cigarettes to scare the public, and falsely claimed that the products were also target-marketed to youth. Those and other false and misleading claims are still on FDA's website.

In preparing for the meetings in July and this week, the FDA instructed TPSAC to focus and report on dozens of nonexistent, minuscule, and

hypothetical risks or dissolvable products, but not to consider the health benefits that occur every time a smoker consumes a dissolvable product instead of a cigarette.

It was wrong for cigarette companies to mislead the public about the risks of cigarettes for decades, but it's far worse when public health agencies knowingly misrepresent the comparable risk of cigarettes and noncombustible tobacco products. Human rights, ethics, science, and public health must not be compromised by abstinence-only policies and anti-tobacco --

[Microphone timed out.]

DR. SAMET: Questions? Neal?

DR. BENOWITZ: You said that hundreds of thousands of people have quit smoking --

DR. SAMET: You'd better speak into the microphone, please.

DR. BENOWITZ: Sorry. I think you made --

MR. GODSHALL: Several million.

DR. BENOWITZ: Right. I haven't had a chance to read your report. But what data do you have on

dissolvables, and where does that data come from?

MR. GODSHALL: Almost every study that was presented here was also cited in my study --

DR. BENOWITZ: No, no, no. Specifically with respect to people have quit smoking using dissolvable products; where does that come from?

MR. GODSHALL: My testimony said that several million people, American smokers, have quit by substituting smoke-free tobacco products.

DR. BENOWITZ: Right.

MR. GODSHALL: Some of them -- and none of them are on dissolvables. That's just the newest of many products coming down the line.

DR. BENOWITZ: Right. But I just wanted to know about dissolvables. Thanks.

DR. SAMET: Tom?

DR. EISSENBERG: If I understood correctly, you said all smoke-free tobacco products are a 2 or below? Is that correct, in your continuum of risk?

MR. GODSHALL: Yes. The ones that are sold in America, yes. I acknowledge that some of the Asian and African smokeless tobacco products are

probably higher.

DR. EISSENBERG: So I'm looking at some of the data from Dr. Stepanov, looking at just nitrosamine content for Ariva and then, say, Copenhagen long cut. And there's an order of magnitude difference in nitrosamine content. But you would still say that they're equivalent in terms of risk?

MR. GODSHALL: The epidemiology studies do not back up and verify this theory that the more nitrosamines that are in a product, the more carcinogenic it is. That's just not found in the epidemiology.

American smokeless tobacco products -- chewing tobacco, Copenhagen -- they may have higher nitrosamine levels, but even the epidemiology studies find that they're 99 percent less hazardous than cigarettes in terms of mortality risk.

DR. SAMET: Patricia?

DR. HENDERSON: We were presented with data for high school and middle school students trying or

experimenting with dissolvables. What is your -- I guess your knowledge on that?

MR. GODSHALL: Well, 20 years ago I campaigned for the Synar amendment to get enacted through Congress that required all 50 states to start cracking down on sales of tobacco products to minors. So we have 50 state laws that ban the sale of tobacco products to minors. The 1998 Master Settlement Agreement banned any tobacco company that was a signatory from marketing to kids. And the Tobacco Control Act bans tobacco sales to minors.

So this whole notion that minors are using these products is just coming from people who are the abstinence-only prohibitionists. Where's the data? Where are the kids that are using these products, and who's selling them?

If the Indiana Health Department has a problem with it, well, the Indiana Health Department should look at itself in the mirror because they're responsible for enforcing the Indiana state law that bans the sale of tobacco to minors. And if Indiana retailers are selling dissolvables to minors, Indiana

Health Department should start enforcing its law, not blame R.J. Reynolds.

DR. SAMET: Tim?

DR. MCAFEE: Well, I have a genuine question for trying to understand your world view around this. You're sort of casting a lot of aspersions that people in public health are intentionally lying and don't really believe what they're saying.

I think, in most of these meetings, we've been pretty straightforward, most of the people, about acknowledging the fact that the individual risk of somebody who only uses a smokeless product is less than -- markedly less than a combustible. There might be debate as to whether it's 2 percent or 10 percent. But I actually don't think there's as much dispute as you're claiming.

The main -- hold on -- the issue that I didn't hear you say a word about, and I'm curious how you respond to, is that the biggest concern is the effect -- that the reality is that most smokeless products in the U.S. are not used -- you're claiming millions of people have switched to these and thereby

quit using combustible. But the reality is, based on surveillance data, that the majority of people that are using smokeless products are also using combustible products, and that we're seeing upticks in the use of smokeless products with -- so I just don't understand other than continued investigation, surveillance, limitations on how things are marketed, et cetera, how you're just dismissing the idea that it's a genuine concern -- and there may be answers -- but that these could in certain instances perpetuate the use of combustible products rather than eradicate them, unless we are careful.

MR. GODSHALL: I don't understand this perpetuation of smoking. It makes no sense. These products are alternatives. Every time a smoker uses a smoke-free alternative instead of a cigarette, they're benefitting their health.

DR. MCAFEE: Well, hold on a second. I mean, there's a huge cohort data coming out of Scandinavia in the last five years looking at tens of thousands of people, where the benefits, particularly to adults that are regular smokers, of cutting down because

they're using smokeless products, is not nearly as exciting as we would like it to be.

So I don't think the one-to-one substitution that just -- if instead of smoking 19 --

MR. GODSHALL: Well, there's been dozens of other studies that find there's a dose-response rate. People who smoke two packs a day are at a greater risk of lung cancer, heart disease, and emphysema than are people that are smoking a half pack a day. And for people to say, oh, no, don't cut back; just keep smoking those two packs a day because if you cut back to five cigarettes a day, it's not going to help your health, that's outrageous.

DR. MCAFEE: So what you're saying is we should just dismiss the recent cohort studies that suggest that that's in fact not the case; it's not a one-to-one correspondence?

MR. GODSHALL: Well, I think you should be careful looking at any study published by Karolinska that's in Sweden because they're notorious for -- they're abstinence-only prohibitionists. They oppose snus use in Sweden. They acknowledge that a

fourth of all Swedish smoking men have quit smoking by switching to snus, and yet they're calling for it to be banned.

So I really have a concern about some of the research that's being done. It's junk science, and I'm very concerned. And I think you should really look. And look at the whole body of evidence. Don't just cherry-pick the data; oh, here's one that has a really high number, so let's put that up on the slide and ignore all the rest of the data; even though the other 30 studies found completely different, we won't talk about them because they don't make a news headline.

DR. SAMET: Okay. I think you've responded to Tim's question.

Any other questions?

[No response.]

DR. SAMET: Thank you. And just as a matter of clarification, in terms of the charge to TPSAC, for this report it's very clear where it is. It sits within Act. And there are no instructions from FDA to this committee; they're instructions from Congress

to this committee.

Our next speaker is Gilbert Ross from the American Council on Science and Health.

DR. ROSS: Hi. Thank you.

It's predicted that one billion people worldwide will die of cigarette smoking during the course of this century. I think that's an issue that we have to confront head-on.

There's never been a randomized controlled trial showing that cigarettes cause cancer or heart disease. All of that data has been accumulated on an observational basis, not interventional. There will never be such an interventional study, of course.

The data from Sweden, and from Norway now, clearly indicates that the use of smokeless tobacco in the form of snus has led Sweden to become the country with the lowest rates of cigarette-related disease and the lowest rates of smoking, not a coincidence. These data have to be taken into account by this committee and by the FDA. The Family Smoking Prevention and Tobacco Control Act gives the FDA, I think, some flexibility to take these data

into account when arriving at their conclusion.

The 45 million addicted adult smokers in this country deserve to be told a simple truth. In Sweden, the government doesn't have to tell them the truth. Everybody knows. Tobacco companies don't have to market their product as a cessation aid or beneficial for health or anything. Consumers do that on their own.

In our country, the government says there's no safe alternative to smoking so there's no safe tobacco product. Now that's, of course, technically true, but it's a disservice. It's misleading. If the government, including the FDA, the CDC, the NIH, simply told the truth about the relative risks of noncombustible products, including smokeless tobacco, dissolvables, e-cigarettes, simply said that these products are much, much less hazardous to your health than smoking, consumers would make their own decisions. Tobacco companies wouldn't have to market it as this or be banned from marketing it as this or the other.

We all remember the behavior of the cigarette

manufacturers in the 20th century. It was a pervasive manipulation and cynical misleading and suppression of science. We now have to come to the 21st century and get over it. The tobacco companies are heading towards reduced risk products, and I think that our government should simply acknowledge the fact that these products are 1/100th, approximately -- or if it's 2/100th. There are no studies on dissolvables. There's no studies on e-cigarettes. There are no randomized controls studies on smokeless tobacco. We have to use the data we have.

Consider the 450,000 Americans who die every year of preventable premature death from cigarette smoking, and be flexible in your messages to the American smoker. Simply acknowledge the truth, and I think the public will vote with their feet.

Thank you.

DR. SAMET: Thank you.

Questions? Comments?

[No response.]

DR. SAMET: Thank you.

Our next speaker is Scott Ramminger from the American Wholesale Marketers Association.

Mr. Ramminger.

MR. RAMMINGER: Good afternoon. I'm Scott Ramminger. I'm president of the American Wholesale Marketers Association, a trade association in Washington, D.C. that represents distributors primarily to convenience stores, and one of the products they do distribute, or one of the product categories, is tobacco.

From our perspective, the issue is fairly simple. These dissolvable products are tobacco products. They are sold behind the counter in a non-self-service environment. They carry the same health warnings as other tobacco products and are taxed the same way other tobacco products are.

Like cigarettes and other tobacco products, the sale of these dissolvable products are age-restricted, something we strongly support, and require proof of age before they can be purchased.

We do, as an organization, support the development of lower-risk tobacco products such as

dissolvable tobacco products. And as managers of the Coalition for Responsible Tobacco Retailing and participants on the board of directors of that organization, we strongly work to make sure that people underage cannot purchase these or any other tobacco products. We are committed to ensuring that tobacco products remain out of the hands of minors.

These dissolvable tobacco products should be treated exactly the same anyway that other tobacco products are in terms of access restrictions and age restrictions. And we believe that adults should have the ability to acquire these products and to choose them instead of cigarettes or other products that are smoked.

That concludes my testimony. Thank you very much.

DR. SAMET: Thank you.

Questions? Comments?

[No response.]

DR. SAMET: Thank you.

Our next speaker is Scott Ballin.

MR. BALLIN: Good afternoon, everybody. I'm

here on behalf of myself. Many of you know me for being a big advocate these days for engagement and dialogue. And so I think this committee is doing a fabulous job in making progress in doing that. My comments are going to be pretty general.

Over the last five years, I've seen a great deal of change, and I actually think we're in a very new era that people are trying to get comfortable with about how we should be approaching the regulation, and not to just tobacco but also nicotine. We need a more consistent environment for regulating nicotine products, smokeless products, dissolvables, and tobacco products, cigarette products.

We need to start thinking in terms of giving consumers and the public better and more accurate information that will allow them to understand the differing risks, relative risks, and the intended uses of the various products that are out there, whether it be NRT, MRTPs, noncombustible products, or combustible cigarettes. People don't understand. There's not enough information to give them an

understanding of what these products are.

I also think we need to get away from the use of the word "tobacco," quite frankly, because all tobacco products are not created equal, and it was mentioned that if -- I would suggest that if an NRT product doesn't make a therapeutic claim, it could be classified as a tobacco product because the nicotine in that product is derived from tobacco, which is the definition of tobacco product.

To move forward, we've also got to get away from the distrust of the industry and put that aside. We've got to have more engagement. We've got to talk about what a product is and what it isn't, less on who manufactures it. I could develop an MRTP, and am I tobacco company because I came up with a novel new product? We've got to change our definitions of how we have looked at this issue for the last 20, 30 years.

In this new era of regulatory oversight, this committee, the FDA, and the private sector has a responsibility and an opportunity to serve the public objectives by doing just that. We don't live in a

risk-free society. We've got all kinds of things out there, and we deal with them as they come up. This committee should look at other centers within the FDA to determine whether they can be helpful in helping you do the work that you do.

So let's be careful about throwing the baby out with the bath water, and begin focusing our attention on developing a more uniform and consistent regulatory policy. If there are problems that need to be addressed, let's address them. If there are labeling issues and packaging issues and other things, let's get them on the table and find out the best way to enforce those things so that the public is served in the right manner.

Thank you.

DR. SAMET: Thank you.

Questions or comments?

[No response.]

DR. SAMET: Thank you.

Our next speaker is Jeff Stier from the National Center for Public Policy research.

MR. STIER: Thank you, and thanks to the

committee for taking not only the comments that I'm making very seriously, but I think it says a lot that the committee is not only having a public comment period, which may be required, but I think the attention and the questions that are being asked tells me that the committee takes seriously its role, not only in reviewing some of the proposals that have been before it and the testimony before it from panel members and experts, but from the public comment period.

I think some of the things that we heard today from all the people that have come out here, I think, speak to the importance of this issue to people across a spectrum. And if I could just take some of my time to help -- and I think Scott did some of this -- but to help kind of bring the tone down a little bit from an accusatory, attacking role that sometimes kind of bubbles up because everyone appropriately feels passionately about these issues, whether it's tobacco harm reduction proponents like myself, or some people who don't necessarily see all the benefits, weighing both sides to allowing

consumers to see the benefits of switching, of using lower-risk products.

If we can just take a moment to lower the rhetoric and recognize that I think we're all here to benefit the public health, and yes, where obviously there are some competing points of view here. But I think at the end of the day, the committee recognizes -- actually, some of the vocal people that have given of their time to speak today, all believe that we need to reduce the risk relating from tobacco. I think if that could be a common ground, we get there.

At the end of the day, there's going to be a point in time when -- and I recognize that TPSAC's role is limited here on dissolvables, and that FDA will eventually have to make recommendations, but at the end of the day, the report that this committee writes will influence FDA, and FDA will eventually have rules. And those rules will affect consumers who are making decisions, not only about whether to use tobacco at all, but how to get off of tobacco. We've seen the people here that have used

e-cigarettes. I think that's very powerful testimony that isn't always being captured in all of the studies.

So I thank the committee for taking this issue seriously, recognizing that this is a very fast-moving area where; if we're focused on dissolvables -- and some of the questions have appropriately redirected back to dissolvables -- recognize, where will we be in five years when we actually have rules in place and people are making decisions in the real world based on limited data, how can we do best to protect public health?

So thank you for your time.

DR. SAMET: Thank you.

Questions? Patricia?

DR. HENDERSON: We're charged not only to look at public health but specifically to look at children and the impact that this has on children.

What is your stance on that? Because you're just mainly talking about adults right now.

MR. STIER: And absolutely it's appropriate

that the committee looks at children and the children who are making choices about what products to use, whether they be cigarettes -- I'd like to see nobody ever smoking cigarettes and nobody ever using dissolvable tobacco, but we live in a world where kids make stupid choices. I think that's -- I don't know. Is there a study on that? Kids make stupid choices, and we want those choices to be based on the best available information.

I don't want kids to start using dissolvable tobacco products. But my concern is that if kids begin using cigarettes and those kids never have accurate scientific information about lower-risk products, where will they be when they're adult? What choices will they be making when they're already addicted to nicotine?

Thank you.

DR. SAMET: Patricia?

DR. HENDERSON: Just to follow up on that, and do you think the industry is ready to move in that direction? Because based on the information that we have, it's not going that direction, at least

based on the industry's document.

MR. STIER: Well, ultimately it's not up to the industry because the law requires that FDA come up with rulemakings and guidance for that. So I think it's important that we take into account children's health. At the end of the day, it's going to be FDA that decides. But I think FDA has an obligation to children to make sure that the information that the agency provides, and allows industry to provide to adults, be based on scientific information. And rather than be concerned about only, will kids ever think -- because what's going on here, I think what the question is, a fair question is, what might happen if kids think dissolvable is not so harmful?

It's a fair question to ask. But you have to balance allowing scientifically accurate information about risky products to be compared to other risky products. And if we're interested in protecting kids, we also have to allow for the availability of accurate information to kids on lower-risk products and not just say, as has been said by some before,

that all tobacco products are harmful, period, when they are -- all tobacco products are harmful at different levels. That's a fair distinction.

DR. SAMET: Tim?

DR. MCAFEE: So I would just ask, do you think it would be fair that we should include in what we share with our children the fact that if they use a lower-individual-risk smokeless product, including dissolvables, their probability of progressing to smoking is higher? Because that is what the data shows so far.

MR. STIER: So I think if the data shows that, I think that information provided to children should be based on the science. I would rather parents tell children never to use any tobacco product or nicotine product at all. But I also think it's important that that information -- based on the concerns for children eventually going up, up to more dangerous tobacco products, I think that information should also be balanced with accurate information about lower-risk products that are available.

We don't want our kids using any tobacco

products at all. But I think you have to balance that with the information that's provided to consumers, being based on science at the end of the day. If there is some information that is bad for dissolvables, let that be. And if there's some information that actually might allow kids to choose to use a product that we don't want them using? If that's what the science says, I think -- as so many people on this panel and as FDA have said, I think we ought to put the science out there and let it fall where it may, even if it doesn't always meet our public policy agenda.

DR. SAMET: Tom?

DR. EISSENBERG: Yes. I respect very much the idea that we should be making these decisions based on good science. I wonder what you and your organization think about the situation where we find ourselves, or the future situation when it comes to new products, where a product that has some acknowledged danger and some potential lethality is released for marketing in the absence of any science provided by the companies that are doing the

marketing. It makes it very difficult to make decisions. And I wonder if that's the sort of situation you want us to continue to find ourselves in.

MR. STIER: Well, I think we find ourselves, and the committee finds itself, and the FDA finds itself, always in the situation where we have to make a decision based on the real world, on limited information. We never have all the information we want.

I think there is information that noncombustible tobacco products are less harmful that cigarette smoking. And I think that consumers, and the consumers that my organization represents, many of whom -- I talk on radio shows about public policy issues. And people don't know. People have never considered that there are less risky alternatives to cigarettes.

I think we owe it to people to put that out there, even without all the information available, whether it's through marketing, whether it's through, obviously, a regulated marketing environment. No,

it's not an easy task. But I think there are down sides to being overly regulatory here by the unintended consequence of a very tight regulatory system, which will absolutely protect kids by never giving them any information about different risks. There's a risk that all people will continue to have not enough good information about the issue.

But I acknowledge that it is a very challenging environment to regulate, but I think you're not being extra-careful by being extra-regulatory, necessarily.

DR. SAMET: Thank you.

We'll move on to our next speaker, Sandra Sulsky from Environ.

DR. SULSKY: Thank you. Environ is a consultancy, and the work I'm about to describe was completed by me and my colleague, Dr. Annette Bachand, under contract between my company, Environ, and two of our clients, R.J. Reynolds and Swedish Match.

Models provide the only short-term option for estimating population health effects of exposure to

products recently introduced to the market. Dissolvables and other modified risk products are in this category.

This slide highlights features of several dynamic population models that have been described in the literature and that could be used for this purpose. A dynamic model is one that allows the population to change its exposure and risk status over some time variable, like age. In contrast, static models are less realistic. They set exposure status once, and it doesn't change with time. So we've highlighted only dynamic models on this slide.

The far right-hand column shows the features of a new model that addresses the limitations of the others and is more flexible and comprehensive. This model is specifically a tool for evaluating potential population-level health effects that might result from increases or decreases in use of tobacco products with different risk profiles.

The model compares mortality in a base case -- for example, a population where the only possible exposure is to cigarettes -- with mortality

in an alternative or counterfactual scenario, where an additional product is introduced, or made available, that is, to the same hypothetical population. It currently estimates all-cause mortality, but will be extended to include specific diseases.

In addition to filing materials to the docket for this meeting, two scientific papers are currently undergoing journal review. We are working towards developing a user interface to make the model available for use over the internet. And two weeks ago we met with Dr. Ashley and colleagues from CTP to discuss the model in some detail.

If the committee feels it would be useful, I can be available to meet with you for a more lengthy discussion than is available today. Thank you.

DR. SAMET: Thank you.

Questions? Neal?

DR. BENOWITZ: In the context that we have very little data on things like transitions from dissolvables to cigarette smoking, or how many people quit, or the dose-response of reduced cigarettes

versus disease, how can you possibly model this?

DR. SULSKY: Well, that's what this model allows. All the input is specified by the user, and so the user sets out the scenarios here she would like to test. So you start with some reasonable initiation and cessation patterns, for example, from the population of concern, let's say the U.S. for ages 13 to 21.

Then you say, well, if we introduce a product and we call it a lower risk product, perhaps some proportion of those who would not have started smoking will start using; here's the proportion I want to evaluate. Perhaps some people who would have started smoking will use this new product instead; here's the proportion that I wanted to evaluate.

You allow those people to age over some user-specified time interval. You specify the excess relative risk that you think is reasonable, or higher or lower, perhaps, than might be estimated for the new product compared to cigarettes, and you see what happens.

DR. BENOWITZ: Well, I'm very supportive of

models. I think it's a great idea. But the problem we have is that dissolvable products have just come on the market. They're hardly used by anyone. And how can we ever have the parameters to make any judgments based on models?

DR. SULSKY: So the model, it's just a way to say what would happen if the situation looks like this, like I wanted to specify. And then it's a Bayesian model, so there are uncertainties associated with the model input that are reflected in the model output. And then over time, as new data become available, those model input parameters can be refined, and therefore the posterior intervals would be reduced.

DR. SAMET: Fred?

DR. PAMPEL: With 33 transitions and imperfect data, that's 33 additional sources of potential error. So is the model work better with the 33 transitions and imperfect data than fewer ones?

DR. SULSKY: What the 33 transitions do is allow for kind of a semi-realistic pattern of tobacco

use over a lifetime or the period of follow-up. So you can model as many or as few of those 33 as you like. It takes a population distribution at the starting point, and it allows people to start and stop and switch and take up dual use over time.

Now, we ran our model using the initiation rates for U.S. males. We happened to use 1980 because of some other reasons around testing the model. So that meant that about -- I think it was about 5 percent of the population was smoking in that age category, which meant that the majority of the population was not exposed to cigarettes.

So actually, as you progress over the time span and look at more than more of those transitions, fewer and fewer people are actually affected by those transitions. So yes, it's propagating error, but the amount of error is relatively small, sort of the tail of that follow-up period.

DR. SAMET: Any other questions or comments?

[No response.]

DR. SAMET: Thank you.

Our next speaker is Dawn Yurkas.

MS. YURKAS: Hello. My name is Dawn Yurkas, and I'm representing myself. I'm a resident of Virginia, I'm a realtor, and I'm a Navy wife. I was asked to speak today as a concerned citizen and address you on dissolvable tobacco products. I'm just an ordinary person with views that represents the average consumer of non-cigarette products.

Former smokers such as myself have turned away from cigarettes to other less harmful smoking alternatives. Being from a military community, many of our friends are choosing dissolvable tobacco products over smoking, as smoking is being banned on Naval vessels and military installations across the country.

In Virginia, dissolvable tobacco products are available to adults over the age of 18. Our state does an excellent job in making sure business operators who sell these products follow the over-18 regulations on tobacco and non-tobacco products. I have been carded to purchase tobacco products and non-tobacco products as a 43-year-old adult, to include even a lighter.

We have an average family where my 15-year-old spends more time on Facebook, texting friends, and playing X-Box than watching television, where the majority of youth marketing is focused. I've never seen disposable tobacco being marketed directly to youth with fancy flavors touted as candy treats or other marketing that I would find inappropriate. And I find a lot of stuff inappropriate.

Anything a person can do to quit smoking and find an alternative, whether it be dissolvable tobacco, an e-cigarette, or a nicotine patch, should be promoted, but not one product over the other. What works for one person is not going to work for someone else in their efforts to quit smoking.

I quit smoking using an e-cigarette after several years of struggling with prescription medicines, nicotine patches, and gum, while friends have used dissolvable tobacco successfully.

Tobacco harm reduction products, including dissolvable tobacco, reduce carcinogens and toxins to the user, lower rates of health issues, eliminate secondhand smoke, and make a vast improvement to a

person's general well-being as well as the environment to the people who live and work around them.

Thank you.

DR. SAMET: Thank you.

Questions? Comments? Tim?

DR. MCAFEE: Yes. I just have a quick question. Thank you for your comments.

I'm basically just curious, what are you kind of worried that TPSAC or the FDA might do about the dissolvables, or is there anything positive that you would like them to do? Or do just pretty much want to make sure that the status quo stays the same?

MS. YURKAS: Well, in our friends that use dissolvables, because many of them are still active duty military or have retired now, with the smoking bans and restrictions, it has allowed them to continue with the nicotine that they'd need, that they've become addicted to, and improve their health.

I would like to see the FDA give a lot of weight and thought to tobacco harm products, and especially do significant research, and really have

something out there that the public can embrace. We all know that smoking combustibles, the act of burning tobacco -- that's how the state of Virginia puts it -- is a health risk. It just is. And for many smokers -- I mean, for me it took 15 years before I found a way successfully to quit smoking.

I quit smoking in September of last year, and I used an electronic cigarette. I've converted 10 smokers to electronic cigarettes from smoking. Several of our friends have gone to dissolvables. I see a lot of stuff in the internet out there in studies that say that it's being promoted to children, and I don't see that it's being promoted to children.

My son goes to a Title I school. It's a 98 percent minority high school. The percentage of children that would use a dissolvable tobacco product in that school are very, very minor. And I don't know if this comes from state regulations and just the fact that, in our community, we're very concerned about minors having access and being able to use products that are not for them.

DR. SAMET: Thank you.

MS. YURKAS: Thank you.

DR. SAMET: Our next presenter is Carl Phillips.

DR. PHILLIPS: I speak today as an educator with an interest in the nature of science and its role in the functioning of our society, and from that perspective I would like to say, won't someone please think of the children? If an impressionable young mind stumbled across how science is often portrayed in this corner of our nation's government, he would be at risk of never becoming scientifically literate, let alone wanting to be a scientist.

First, science is supposed to be a honest, truth-seeking process that attempts to figure out the best possible answer to a question, often via methods that require innovative thinking. Our impressionable young mind, however, might come away believing that science consists of just following a few narrowly defined recipes rather than taking in all the best information we have, in myriad forms available from various forums, and thoughtfully making the best use

of it; believing that health science focuses on looking only under street lamps and obsessing about easy but not directly informative work like chemistry, rather than trying to do the more difficult work to translate that into actual health effects.

From today's session, he might learn that science involves such methods as manipulating children into giving the answers you want; speculation-laden anecdotes; limiting reviews of the evidence to exclude any evidence you wish did not exist; and counting unsupported assertions by authors as evidence. And it would be taught that science is not about identifying how we maximize our knowledge, but that it involves declaring that we just don't know anything when in fact we know quite a lot.

Our impressionable young mind is not going to think very highly of science, and he might reasonably conclude that the best way to become involved in America's version of science is to go to law school, which of course means that this misguided way of looking at science may be a gateway to more dangerous

behaviors.

Second, this poor child would get the impression that a hypothetical cardiovascular condition or cancer that occurs 40 years from now will be just as harmful as a near-term case in a current smoker, a case that's caused because this smoker was discouraged from switching to low-risk alternatives as a matter of official policy.

Do we really want to tell that child that we expect so little of his generation's health science that a 40-year-out cancer will be no more treatable than one that would occur today?

Finally, at the very least, I would urge the committee and the center to make sure that any of such anti-scientific writing is kept in childproof packaging rather than being left laying around on the internet where anyone could stumble across it and possibly permanently damage their developing minds. Thank you.

I've never received any funding in support of my work as a historian of science. And I got here today because KSAA (ph) paid the two-figure cost of

that.

DR. SAMET: Thank you.

Questions or comments?

[No response.]

DR. SAMET: Thank you.

Our next speaker is Elaine Keller, the Consumer Advocates for Smoke-Free Alternatives Association.

MS. KELLER: My name is Elaine Keller, and I have no conflicts of interest to declare other than the fact that I have been smoke-free now for nearly three years thanks to switching to a smoke-free alternative.

Dissolvable tobacco products are receiving unfounded criticisms that discourage smokers from switching to this less hazardous alternative. In Sweden, increased use of snus has lowered both the smoking rates and the total tobacco use. Between 1981 and 2007, the percent of smokers fell dramatically, while snus use increased slightly. Increased availability of a variety of acceptable smoke-free alternatives could have a similar impact

on U.S. smoking rates.

Dual use does not equate to harm escalation, necessarily, for two reasons. Smokers who use a second product reduce their smoking, and they're much more likely to stop smoking altogether if they know that what they're switching to is less risky. Last July, TPSAC was led to believe that a young child died from ingesting a dissolvable tobacco orb. In truth, there were no tobacco product child fatalities of any kind during that three-year period.

Using candy as an adjunctive for a product that is intended for and used by adults, that is not marketed as candy, that is not shelved as candy, that is not labeled as candy, is misguided and dangerous. There could be tragic consequences to doing this.

FDA is required to consider the net effect on public health, taking into consideration uptake by non-users. Smoke-free alternatives may be up to 99 percent less hazardous, but let's be conservative and estimate using a 95 percent risk reduction.

Switching all smokers to a product 95 percent less hazardous would save over 400,000 lives

annually. Even if all non-tobacco users began using the product, which is highly unlikely, the net effect on public health would still remain positive, saving over 3 million lives in the next 10 years alone.

If you convince that all tobacco products are equally hazardous, they will conclude, I might as well smoke. It's time to start educating consumers about the health benefits they can realize by switching to less hazardous alternatives.

Members of this committee have an awesome opportunity. You can save millions of lives by refusing to give in to pressures to outlaw safer alternatives.

Thank you.

DR. SAMET: Thank you.

Questions? Comments? Tom?

DR. EISSENBERG: Thanks for that testimony. I agree with you that these products, the dissolvables, shouldn't be called candy. I was struck by the presentation from the woman from Indiana, where she put up the picture; you may have seen it. And I had not seen pictures like this

before, so I guess I was struck by the fact that -- pardon me for saying it -- that they do look like candy and they're packaged as though they were candy.

Help me with that. What should be done about that?

MS. KELLER: Well, I think it's insane to be promoting -- putting pictures like that up on the internet where children can see them because you're convincing the kids, hey, this stuff is candy. We should be telling them, it's a tobacco product. We should be warning the parents, this is what the packages looks like. This is what Stonewall and Ariva look like when you take them out of the box. So keep your eyes peeled, parents, and watch what your kids are doing.

DR. EISSENBERG: Do you think it would be less likely to see pictures like that on the internet if there was some either voluntary or enforced discipline on the tobacco companies not to make them look this way?

MS. KELLER: The tobacco companies aren't

putting those pictures up next to candy. This is being put up by the -- oh, the public health people, the committees against smoking, and what have you. The very people who are supposed to be helping to keep youth from using tobacco products are doing things that promote the use of it, and that's sad.

DR. SAMET: Any other questions or comments?

[No response.]

DR. SAMET: Thank you.

Our next presenter is Linc Williams.

MR. WILLIAMS: My name is Linc Williams, and I have no conflict of interest.

I've been many things in my life. I'm a husband, a father. I was a corpsman in the United States Navy, a firefighter, a paramedic, and an active volunteer in my community. And I'm proud today to add to that list as ex-smoker after 22 years of smoking.

I smoked for 22 years, and for the last 15 years I've tried to quit. My wife and I went through and added up the attempts. I have tried the patch five times. Lozenges, twice. Nicotine gum,

four times. The nicotine inhaler, once. Chantix, twice. And cold turkey, three times. After my last attempt with an approved cessation and adverse effects from Chantix, I had given up on quitting. I was convinced that I was going to die a smoker.

About 18 months ago, I picked up an e-cigarette in a half-hearted attempt to just merely cut down from a four-pack-a-day habit, to try and reduce that. Within three months, I was tobacco-free. I used both dissolvables and an electronic cigarette to slowly reduce my dependency on actual physical cigarettes. Over the course of three months, I am now off of tobacco products completely, whether cigarettes or dissolvables. I've lost 65 pounds. I no longer have to take medication to control my blood sugars.

So there are a lot of people that say these effects, and what does it do? I'm a real person that's been affected by this, and there are real effects to it. And yes, I know the risk of using an e-cigarette. I know that things aren't known out there. But I, as a non-scientific person, can tell

you, just from the pure using of the device, that I feel the difference, and I can make that informed decision that I'm willing to take the risk that this is better than smoking.

Some of the groups, I'd like to invite them to come out of their ivory towers and look at what it really is to be nicotine-addicted, to talk to the people that are in it in day-to-day life situations, because it is very hard when you're in an environment where all the medical help and advice you receive is, go to the approved cessation devices. If it's not the patch, the lozenges, or Chantix, you shouldn't be doing it.

To me, that's irresponsible medical advice. There are a category of people in this world that are addicted to nicotine and most likely will never give up nicotine. And as medical providers, I think it's irresponsible to not do that.

So I'm going to leave this. My daughter actually asked me the question, and I apologize -- my daughter asked the question --

[Microphone timed out.]

DR. SAMET: I think you're done, actually. But thank you, and sorry that we can't hear about your daughter.

Let's see. Questions for our speaker?

MR. WILLIAMS: (Comment off mic.)

DR. SAMET: Okay. Go ahead and tell us about your daughter.

[Applause.]

MR. WILLIAMS: My daughter was the first one to recognize the difference in my health, my energy, my general change of it. So when she asked me why I was coming here to testify today, I explained that I wanted to explain my effects on it, and that there was a possible consideration to remove these products from the market. And her question that she wanted me to ask was, "Daddy, why would they take it away and have people go back to smoking?"

I'm not expecting you to answer the question today, but I would like you to think about how you would answer that question. Thank you.

DR. SAMET: Do you want to offer up any clarification here or -- I mean, our charge is

actually to review evidence related to dissolvables and write a report, really; nothing to do with on or off market, just for clarity.

Fred, did you have -- I think we have a question.

DR. PAMPEL: What is it about dissolvable tobaccos that worked that nicotine replacement therapy didn't work? I mean, you talked about addiction, but both of those addressed the addiction. Why one and not the other?

MR. WILLIAMS: I can't give you an exact answer on it. But there is a huge difference between putting on a patch and getting a steady dose of nicotine. My life cycle does not revolve around nicotine 24 hours a day. It's about stress management, certain periods of my day that -- first thing in the morning, after a very stressful meeting with my boss. Those are the times I wanted nicotine. I didn't really want nicotine constantly, like a patch would give.

Unfortunately, the lozenges give you a very horrible taste. I was one of the people that it

caused incessant hiccups in. But even though it gave me hiccups, I still took it because I really wanted to quit. But it didn't, unfortunately, satisfy that craving that was there, especially during high stress periods of my life.

Now, the dissolvable I could take when I want. It was almost instantaneous relief of it or cessation feeling. And I could control when I wanted it. It wasn't a constant 24 hours. And it worked.

DR. SAMET: Ellen?

DR. PETERS: I was just curious. You said you also used the e-cigarette, I believe?

MR. WILLIAMS: Yes.

DR. PETERS: Do you continue -- you said you stopped using dissolvables. Do you continue to use the e-cigarette?

MR. WILLIAMS: I still continue to use the e-cigarette, yes.

DR. PETERS: And why do you do that?

MR. WILLIAMS: Because I enjoy it, and it's just a pure effect. I am still a nicotine addict. I still use nicotine. Now it's a low-dose nicotine.

I've gone from a very high dose of nicotine in an e-cigarette down to an extremely low, to where I'm pretty confident I could cut it over the next three months or so down a zero. But I still enjoy it. And that's one thing no cessation product to date has been able to address. Smoking is an enjoyable experience for a smoker.

DR. SAMET: Thank you.

Next, and last, Justin King.

MR. KING: Hello. My name is Justin King. I have no conflict of interest to declare.

I'd like to start off by talking a little bit about my family. My grandfather took his own life while living with emphysema, which was caused by smoking cigarettes, and my grandmother died of lung cancer from smoking cigarettes.

I smoked for 18 years, and two years ago I was smoking two packs a day. I was killing myself slowly at $300 a month, a cost of $300 a month. I'm now 75 pounds lighter, two years later. I run about 10 miles a week now. And I've been smoke-free for two years.

I wouldn't have been able to -- I don't feel like I would have been able to quit smoking if it wasn't for the use of electronic cigarettes and dissolvable tobacco products. I'm scared that the transformation that I've undergone may be denied to other people because these products are not available to them or will not be available to them. They provide a smoke-free alternative option for people like me who feel they cannot or do not want to stop the use of nicotine.

I sometimes feel like organizations are attacking these smoke-free alternatives, even though certain government organizations preach against smoking. I find it ironic that this occurs, and I don't understand why it's happening.

There are much less hazardous alternatives available to smokers who can't quit, and I think that we need to fight to make them available so people don't have to die terrible, needless deaths, the way that people in my family did.

Thank you.

DR. SAMET: Thank you.

Questions or comments? Okay.

Oh, Tim? Sorry.

DR. MCAFEE: I'm just curious if you could help us where that feeling comes from. I run the Office of Smoking and Health at the Centers for Disease Control, and I can certainly tell you that we have no budget to try to make you feel bad about using these products.

I know that the tobacco industry spends almost a billion dollars a year promoting smokeless products. I don't know what percent of that is related to dissolvables, et cetera. And I know that the e-cigarette companies are spending a lot of money promoting them.

I know there are somewhat random statements that are said, and they run in a newspaper for a few moments. But as I look at the world, our capacity to make you feel guilty, et cetera, is pretty limited compared to the tobacco industry, the e-cigarette companies.

Most of our concerns, I think, as people have listened to them today, are far more oriented around

making sure that there's not unintended consequences related to children. I think the FDA might have worries around e-cigarettes in terms of contaminants, so that if you were to use them, there might not be horrible things that were happening that people didn't know.

So I'm just curious where the feeling that you're about to have your capacity to do this is coming from? Where are you seeing this?

MR. KING: Where am I seeing where this feeling comes from?

DR. MCAFEE: Yes. Where is all this information coming that's trying to make you think that you shouldn't have done what you did, or that these are going to get taken off the market, et cetera?

MR. KING: Oh, okay. So why do I feel like there's a jeopardy that smokeless alternatives will be taken off the market?

DR. MCAFEE: Or that there's this massive publicity that's much bigger than the billion dollars that the smokeless tobacco companies are expending?

MR. KING: I think I'm having a hard time locking down exactly what your question is.

DR. MCAFEE: Well, you had closed by saying that you felt that there's a "we" out there that's trying to make you not -- that's trying to de-legitimize your success at doing this, and take it away so that other people can't do it?

MR. KING: I'm just trying to get the question to be asked a little bit more clearly.

I think the reason that I feel that way is because of the FDA's trying to ban the use of e-cigarettes in the United States. And I feel that that struggle -- that there has been a struggle that people who use e-cigarettes have had to try to make sure that option is available to the public. And that's why I feel that way, because I feel that those bans are going to stop people from being able to choose this alternative.

DR. MCAFEE: Do you think it's inappropriate for them to regulate them?

MR. KING: No.

DR. SAMET: Okay.

DR. DEYTON: Just for clarity's sake, Judge Leon's court ruling was quite clear. FDA does not have jurisdiction over e-cigarettes at this time.

MR. KING: Right.

DR. DEYTON: And so there's no attempt that FDA is trying to ban any product that we don't have an authority over.

MR. KING: Right.

DR. DEYTON: So I'm trying to clarify to make sure that the public record is as clear as possible.

DR. SAMET: Okay. Thank you.

Any other questions or comments?

[No response.]

Committee Discussion

DR. SAMET: Well, let me say thanks to all the public speakers.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Now, we've actually heard from RTI, which was originally scheduled to come after the open public hearing. I think there's several things we could do now.

One is reflect on anything we've heard during the open public hearing; and second, I think, get a little bit organized for tomorrow because tomorrow we need to shift from being passive recipients of a lot of knowledge to thinking about what we're going to do with it, and moving towards talking about writing our report, which I think everyone knows, and we were recommended at the start of the meeting it's due on March 23rd.

Tomorrow we have a lot of open time to have discussion. We will have some input tomorrow from the Virginia Foundation for Healthy Youth and also from Mark Wolfson at Wake Forest. But most of our time is for us to discuss. There's a somewhat brief note that I put together help guide our thinking, and a figure, but that's really for the purpose of discussion.

I think tomorrow we'll also have some

discussion about what the form of the report might be, unless we have enough time to initiate that now. That's another possibility. But perhaps we should just wait till tomorrow with fresh minds, fresher minds.

So perhaps we should -- we can wait till tomorrow to do that.

I note that the adjourn time is listed as 4:00 p.m. Inexplicably, some of us have planes that will require us to leave a little bit earlier than 4:00 p.m., and I know we will be forgiven by the higher authorities. And I suspect that probably that means we'll be ending at roughly 3:00, or you can continue without the chair and other committee members.

[Laughter.]

DR. SAMET: That's our confession.

John?

DR. LAUTERBACH: Dr. Samet, I'd like to ask a question of Dr. Eissenberg and Dr. Benowitz to clarify something I thought I heard them here in the exchange with the people that were giving public

testimony.

I think I heard is, we don't have enough information between Swedish snus and dissolvables. And if that indeed is -- and I heard that correctly, I'd like to have the doctors explain to me what particular factors they need.

Is it a question of tobacco chemistry? Is it a question of toxicology? Could you gentlemen please clarify if that indeed is the feeling?

DR. BENOWITZ: I can certainly say from my perspective, it was the transition data, like how many youth are going to start? What's the transition from dissolvables to smoking cigarettes? How many people who are smokers who use dissolvables are going to quit smoking? How many people are going to use dissolvables to keep on smoking instead of quitting? If there is a reduction in cigarettes, how do we translate reduction of cigarettes into change of health risks?

Those are all transitions that I don't think we have any data for.

DR. SAMET: There's this famous quote that

always come up at this point by the statistician Box, which is that, "All models are wrong but some are useful." And I think the point that Neal was getting at in his exchange with Dr. Sulsky was, when do you have enough certainty about enough of the parameters? If you have created a model complicated enough to have 33 parameters for which you need estimates, regardless of elegant tools like Bayesian approaches for dealing with uncertainty -- the thing will just blow up I think is really the question. And I think the question is whether one can trust the answers.

That's what we're getting at. Remember, we did use modeling in the case of menthol and sort of a far simpler approach. I think that was what the discussion was about. I actually do think the models are very useful for saying what it is you would like to know, and it really forces you to come to some specificity. And I'm sure that FDA is going to be using models as a tool.

But I think that's what the exchange was about. And I think part of our work in writing the report will be to say, well, how much do we know, in

a sense, about some of these points of transition? So a little bit of that is in the figure that I constructed, in fact a far simpler figure than what underlies the Environ model.

Is that fair, Neal?

I think Tom, do you want to weigh in on this?

DR. EISSENBERG: Yes. Thanks for the question.

I think what I'm going to say has to do with exactly the same topic, the transitions. I actually wrote it down in a sentence I wasn't planning on reading aloud, but it was to help me crystallize my thinking. And this was yesterday when I got back to the hotel. So I'm going to go ahead and read it since I wrote it.

"The heart of the Swedish experience is a complete substitution of cigarettes with snus. There is no systemic empirical published evidence that dissolvable tobacco products will substitute in like manner. Instead, all existing scientific evidence suggests that these products will supplement and not substitute for cigarettes."

Now, it's an open question, the extent to which partial supplementation of dissolvables, in a way that reduces cigarette use to some lower level than somebody had, will result in a health benefit. And I simply -- I don't know anything about that.

What struck me as critically important yesterday is complete substitution was at the heart of the Swedish success. And if you show me data that are generalizable, that are systemically collected, that demonstrate that people in this country will use dissolvable products in a way that completely substitute for combustible tobacco, then I will stand up and trumpet to the world that these are likely harm reduction products that we should be advertising as such.

I don't see those data. Show me those data.

DR. SAMET: Okay. Let me ask if there are other reflections on what we've heard today in our session, our open public hearing session and the other presentations. Neal, and then Tom.

DR. BENOWITZ: I just want to go back a point that was mentioned in one of the presentations. We

haven't talked about it. Where are we in developing a definition of dissolvable products?

DR. SAMET: Well, I think we can keep that right on the list for discussion tomorrow. We've heard about lack of definitions, for sure, but we haven't heard the counter to that or the need to have one. And I think that's probably where we need to start the discussions. I think it's an important point, Neal, and one clearly we're going to come back to.

Yes, Tom?

DR. EISSENBERG: What I heard from the public discussion, a common theme across several speakers that I took away, was the need to carefully evaluate the labeling and the advertising messages that accompany dissolvable tobacco product sales.

I think I saw, in reviewing our questions, several questions that address labeling and marketing issues. And so I think, when it comes to attending to the public testimony, we should pay careful attention to those issues because it seems to be something that really strikes a chord.

DR. SAMET: Others? Let's see. Mark and Arnold, you've been silent.

DR. CLANTON: Nothing to add.

DR. SAMET: Nothing to add? Mark, you're unusually silent when you're at a distance on the phone.

DR. CLANTON: Yes. That's probably because I'm at a distance on the phone.

MR. HAMM: And I have no comment, either.

DR. SAMET: All right.

Anything else before we break up?

DR. LAUTERBACH: Dr. Samet?

DR. SAMET: John, please.

DR. LAUTERBACH: This is not related to dissolvables, but Dr. Deyton said something on e-cigarettes that I didn't fully understand. I know it's of concern to a lot of people about what the FDA could do on e-cigarettes or can't do.

DR. DEYTON: Yes. Thanks for the question. So before the Center for Tobacco Products was established, before the law, the setting up the center was passed and signed by the president, FDA

evidenced some concern about e-cigarettes and took some actions. I wasn't here then, so I don't actually -- I actually can't speak to that.

But that was challenged, and that was taken to court. And a federal judge ruled on that, and basically said -- and I'm paraphrasing here, and I'm not a lawyer. I'm just a doctor; I'm not a lawyer. And that judge said that -- and subsequent to the earlier FDA action, the Tobacco Control Act, passed, and it gave FDA authority over tobacco products used for "under the law, human consumption," which I translate in my non-lawyer leeway as for personal use as opposed to therapeutic of medicinal use.

Judge Leon said, I think very clearly, FDA has authority over tobacco products when they're used for a therapeutic purpose -- that is, to treat nicotine addiction -- and now that FDA has authority over tobacco products used for "human consumption," FDA should figure out how to do all of it.

So today, FDA has authority over tobacco products when they're used for treatment of nicotine addiction in our sister agency, Center for Drug

Evaluation and Research. And the Center for Tobacco Products has regulatory authority directly over cigarettes, cigarette tobacco, roll-your-own, and smokeless tobacco.

We have indicated our intent to consider regulatory approaches for tobacco products for which we do not currently have direct jurisdiction.

Did that help at all, or did I confuse you?

DR. LAUTERBACH: No, no.

DR. DEYTON: And e-cigarette would be in that former category.

DR. SAMET: Okay. Thank you.

Let me see. Any last items before we end?

[No response.]

Adjournment

DR. SAMET: Okay. Then we are adjourned. Thanks. And remember, tomorrow we're back at 8:00 a.m.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)