The Workshop met at the White Oak Conference Center, Building 31, Room 1503, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:30 a.m., David Ashley, Ph.D., Director, Office of Science Center for Tobacco Products, Cathy Backinger, Ph.D., M.P.H., Deputy Director for Research, and Andrew Holtz, M.P.H., Workshop Moderator, presiding.

PRESENT:
DAVID ASHLEY, Ph.D., Director, Office of Science Center for Tobacco Products, FDA
CATHY BACKINGER, Ph.D., M.P.H., Deputy Director for Research, Office of Science Center for Tobacco Products, FDA
ANDREW HOLTZ, M.P.H., Workshop Moderator
ANTHONY P. ALBINO, Ph.D., Vector Group Ltd.
MICHELE BLOCH, M.D., Ph.D., Tobacco Control Research Branch (TCRB), Division of Cancer Control and Population Sciences (DCCPS), National Cancer Institute (NCI), U.S.
CHARLES GAWORSKI, M.S., DABT, Altria Client Services

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PRESENT(Cont'd):
SCOTT L. TOMAR, D.M.D., M.P.H., Dr.P.H.,
College of Dentistry, University of Florida
JEFFREY WILLETT, Ph.D., Tobacco Control
Program, New York State Department of Health
LOIS BIENER, Ph.D., Dana-Farber/Harvard
Cancer Center, University of Massachusetts, Boston
MONICA J. GRAVES, M.B.A., The R.J. Reynolds
Tobacco Company
MANOJ HASTAK, Ph.D., Kogod School of
Business, American University
PAMELA LING, M.D., M.P.H., Helen Diller
Comprehensive Cancer Center, University of California, San Francisco
SAUL SHIFFMAN, Ph.D., Department of
Psychology, University of Pittsburgh; Pinney Associates
DAVID ABRAMS, Ph.D., Steven A. Schroeder
Institute for Tobacco Research an Policy
Studies at Legacy; Johns Hopkins Bloomberg
School of Public Health; Georgetown
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MICHAEL F. BORGERDING, Ph.D., The R.J.
Reynolds Tobacco Company
CRISTINE DELNEVO, Ph.D., M.P.H., School of
Public Health, University of Medicine and
Dentistry of New Jersey
WILLIAM C. MAIER, Ph.D, M.P.H., REGISTRAT-
MAPI
MARK PARASCANDOLA, Ph.D., Tobacco Control
Research Branch (TCRB), Division of Cancer
Control and Population Sciences (DCCPS),
National Cancer Institute (NCI), U.S.
National Institutes of Health (NIH)
Welcome Day 2 by Mr. Holtz 4
Panel 3: Modified Risk Claims for Reduced Substance Exposure
   Invited Panelists:

   Dr. Anthony Albino
   Dr. Michele Bloch
   Mr. Charles Gaworski
   Dr. Scott Tomar
   Dr. Jeffrey Willett

Panel 4: Consumer Perceptions of MRTPs
   Invited Panelists:
   Dr. Lois Biener
   Ms. Monica Graves
   Dr. Manoj Hastak
   Dr. Pamela Ling
   Dr. Saul Shiffman

Panel 5: Postmarket Surveillance and Studies of Commercially Marketed MRTPs
   Invited Panelists:

   Dr. David Abrams
   Dr. Michael Borgerding
   Dr. Cristine Delnevo
   Dr. William Maier
   Dr. Mark Parascandola

Adjournment 325
P-R-O-C-E-E-D-I-N-G-S

8:32 a.m.

MR. HOLTZ: Good morning. And now to the second and final day, of this public workshop on the Scientific Evaluation of Modified Risk Tobacco Product Applications. With the Food and Drug Administration.

A couple of reminders. The website for more information about this workshop and related information is www.fda.gov/tobacco. And also, as you see on the screen, the docket for submitting comments is open until September 23rd.

So that's one of your opportunities to submit your own comments on what we're discussing here today, about how the FDA should act on the legislation giving authority over tobacco, including any claims relating to modified risk in tobacco products.

If you have any trouble submitting comments or have other questions, I want to give you an email. The email is not for Neal R. Gross & Co., Inc.
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submitting comments, you do that on the website there. But an email for questions if you have trouble is workshop.ctpos@fda.hhs.gov. And again, you have until September 23rd to submit your comments.

We have three panels today and I will keep us on time because I know a lot of people want to escape before Hurricane Irene arrives.

Let's see, we are now at Panel Number 3. Okay. So we're going to be talking about the Modified Risk Claims for Reduced Substance Exposure. And I'll introduce the panelists one at a time and then they each have a few minutes to offer some brief, not comprehensive at all, opening comments.

The first speaker will be Anthony Albino, PhD. He's a research professional with over 40 years of broad experience in both basic and clinical cancer research in public health.
Dr. Albino graduated from Hunter College in New York City with a B.A. in biology in 1970. He received his PhD from Cornell University in 1974, with a focus in RNA tumor viruses.

He's held research positions at several New York City medical institutions, including 22 years on the staff of Memorial Sloan-Kettering Cancer Center.

Dr. Albino also held the positions of director of research and deputy director of the Cancer Center at the American Health Foundation, an institution dedicated to understanding the role of tobacco in human diseases and to promoting cancer prevention initiatives.

In 2001, Dr. Albino became a senior executive for Vector Group Ltd., and its subsidiary, Vector Tobacco Incorporated. Dr. Albino has also served as a member of the Commission for a Healthy New York.

A panel of experts in the field of
tobacco control, science, health promotion and community intervention that reported directly to the Commissioner of the New York State Department of Health and the Governor of the State of New York.

The mandate of this Commission was to understand and reduce the burden of tobacco usage for New York State residents. Dr. Albino.

DR. ALBINO: Thank you. Well good morning, all. I'll be particularly brief because of the weather. I just want to make a few salient points.

I'm just going to focus my brief remarks on the last question, that's in bold here. I think the most important point here, of course, and the bulls-eye of all these meetings, is this measurable and substantial reduction in morbidity and mortality as related to reduced risk tobacco products.

This is the most important point as far as I'm concerned. The dedicated use of
MRTP must be capable of directly reducing the morbidity and mortality historically associated with the cigarette, if you used throughout a smoker's history.

Alternatively, if it's a smoker who's been a current smoker for many years, an MRTP must be capable of interdicting the natural course of a pulmonary disease or cardiovascular disease at a point when this trajectory can still be altered.

And this will be the tricky part and we can discuss this in more detail later. But really what it means is that we're going to have to have stratification between patients in the clinical trials between the new user MRTPs and users of conventional cigarettes that switch to an MRTP.

Now the disease risk can be altered at any one of these stages. And it's very easy to, in my opinion, to look at exposure and internal dose. Alternatively it's very easy to look at the molecular and
cell dysfunctions as they relate to disease.

The hard part is linking up the
top to the bottom, and especially dealing with
this middle one, this manageable biological
damage. We're learning over the last ten
years that there's a lot of damage that's
caused by all kinds of environmental insults,
including tobacco.

Much of it is irrelevant, and we
can't be fooled by looking at damage. We have
to look at the damage that's actually driving
the disease. And the technology now is
available to kind of do that.

I'll just briefly go through this.
In terms of looking a quantitative analysis of
the harmful, and potentially harmful,
ingredients. I think looking at levels in the
products that are delivered in smoke, or the
levels that are delivered to smokers, or the
levels in metabolites in smokers.

I think the technologies are
there. More can be gained, more can be
generated in dialogue with the industry. And
we think that's relatively pretty easy to do.

The hard part is looking at the
clinical impact of these kinds of cigarettes,
because they're very difficult to assess. So
you can read why.

But the most important thing here
is that, I think now the time has come where
it's very doable by not using the old kind of
paradigm, the EPA kind of paradigm.

We're really more using advanced
programs and systems biology, bioinformatics,
microarray technology, total genome sequencing
and so forth. Those techniques are very
powerful and can tell us a lot about the
global impact of cigarettes.

Insight to and in vivo in subjects
at all stages of their smoking history. And
then moving on the Phase II and Phase III
clinical trials.

We know how to do this with the
FDA guidance, it's an approachable thing. And
with modern technology we really feel we can
get some serious answers about the impact of
any kind of cigarette product.

But just a caveat, we must retain
a healthy skepticism about using a surrogate
endpoint biomarkers. Just because a surrogate
endpoint biomarker moves with a particular
exposure doesn't mean it's causal.

It doesn't also mean that if it
goes up or down there's going to be an
improved clinical outcome. So for a clear
biological relevance we have to worry about a
lot things. In terms of it's, you know, it's
measurable, it's quantifiable, it's modulated
by the MRTP.

Very importantly it's on the
causal pathway of the disease, I think that's
very important. We need to really link the
biomarker with the disease state, either pre-
malignant or malignant or whether it's
cardiovascular or not.

And there's a lot of requirements
we need prior to taking the surrogate endpoint biomarkers to the clinic. And there has to be a lot of development and validation. All of this is doable. We have the technology, we have the skills, we have the knowledge base in consultation with the FDA.

We really feel now, using modern technology, and stratifying patients in robust clinical trials. Multi-center clinical trials, we can get the kind of answers we're all looking for. Thank you.

MR. HOLTZ: Thank you. Our next speaker is Dr. Michele Bloch who is the acting chief of the Tobacco Control Research Branch at the National Cancer Institute at the National Institutes of Health.

Dr. Bloch has served as a program director in the research areas of women and tobacco, tobacco industry documents, international tobacco control and prevention and other areas.

She oversaw the successful
implementation of NCI's tobacco industry
document research program announcement. And
played a key role in developing and
implementing the NIH's first research
initiative devoted to international tobacco
research and capacity building.

Dr. Bloch's research activities
have included working with the National
Institute of Child Health and Human
Development's global network for Women's and
Children's Health Research to conduct a survey
of pregnant women's knowledge, attitudes and
behaviors regarding tobacco use and second-
hand smoke exposure in nine low and middle-
income nations.

She also helped to develop and
implement NCI's smoke-free meetings polity.
She is the author of numerous publications for
scientific and lay audiences. Dr. Bloch.

DR. BLOCH: Thank you very much.
And thank you very much for FDA for inviting
us here today. In my talk I want to pick up
on the question of assessing individual risk
and comment on what I think is the diversity
of individuals.

The first point I want to make is
this is, we're really dealing with a very
heterogeneous group of smokers who can be
subdivided by age, the elderly are not the
same as the young. By race/ethnicity, by
health status, both those with and without
tobacco induced disease or with other disease
entities, by gender.

And the one that I want to focus
on today is reproductive status. And in
particular the issue of tobacco induced harm
to pregnant and nursing women. Although I
won't deal with reproductive and developmental
issues for men, these are also very important.

And I want to being by commenting,
as I think most in this audience know, that a
little under 20 percent of all women are
cigarette smokers. Slightly lower among women
under 18 to 24, but very significantly higher
under 25 to 44. And our best estimate is that about 13 percent of pregnant women smoke during their pregnancy.

Importantly, about as much as a quarter of all women quit smoking when they learn they're pregnant. And that's something I'll come back to.

This data is a little bit dated, but really hasn't changed very much over the years. We have a little more than six million pregnancies in the United States every year.

Four million of them end in births.

Others are in elective abortion or spontaneous abortion, but a very important point is only about half of pregnancies in the United States are intended or planned, which means that, from my perspective, all reproductive age women are potentially at risk of becoming pregnant.

Because, even though they may not be planning a pregnancy, half of all pregnancies are unplanned. And this is either
because of using ineffective contraception or using contraception poorly, or simply not using it at all.

Now the embryonic period, which is the very earliest stages of pregnancies, is actually among the most critical. That's when organogenesis occurs. And this is actually during the period which a pregnancy is most easily disturbed and most easily subjected to toxicants, both those from cigarette smoke and other insults.

So this whole issue of this early phase of pregnancy and the fact that women aren't necessarily planning to become pregnant makes the issue of reproductive and developmental harm of tobacco use important for all reproductive age women.

I won't review this slide except to say that the significant health effects of tobacco smoking during pregnancy are well reviewed in both the 2004 Surgeon General's report and confirmed and extended in the 2010
But I do want to point your attention to Chapter 8 of the 2010 Surgeon General's report, which does a very elegant and thorough review of what is known of the mechanisms of the health effects of smoking during pregnancy.

It points particularly to carbon monoxide, to nicotine to polycyclic aromatic hydrocarbons, to various metals. And then makes a broad comment about other potential smoke toxicants. And it makes a number of specific chapter conclusions.

Again, about nicotine PAHs and carbon monoxide, which are those that have the most evidence as the potential harm to fetal development.

So I would just conclude by saying that the assessment of potential MRTPs needs to consider the very broad diversity of tobacco users.

One group in particular is the
adverse reproductive and developmental effects for pregnant women, which are really applicable to women of reproductive age, who form a large number of smokers.

We know that tobacco smoke contains many known or suspected reproductive developmental toxicants and that the evidence to date is strongest for carbon monoxide PAHs in nicotine.

But there's really quite a bit of work to be done in this area and it's not an area that receives, in my opinion, as much attention as it needs to. Thank you.

MR. HOLTZ: Thank you. Now we have Charles Gaworski, M.S. DABT. He's currently a senior principle scientist in the Tobacco Regulatory and Health Sciences Organization for Altria Client Services, which provides professional services and support to Altria Group and its operating companies.

His responsibilities include development of the scientific content
supporting regulatory engagement with the FDA and the Tobacco Product Scientific Advisory Committee regarding issues such as harm reduction, new product approvals and related technical issues such as product standards and constituents.

Mr. Gaworski has more than 35 years of experience in toxicology with the majority of that time dedicated to the areas of inhalation and chemical risk assessment.

For the past 22 years he has worked on tobacco related health issues while employed with either Lorillard Tobacco Company, Philip Morris USA or Alcs.

He has authored more than 30 scientific publications, with many of these addressing the potential impact of ingredients on tobacco smoke toxicity.

He received his bachelor's degree in chemistry from Southwestern Minnesota State University. And a master's of science degree in toxicology from Utah State University.
He's also a diplomat of the American Board of Toxicology as a member of the Society of Toxicology and the Society for Risk Analysis. Mr. Gaworski.

MR. GAWORSKI: Thank you. And good morning to everybody. I'm here today on behalf of Philip Morris USA and U.S. Smokeless Tobacco Company to join this discussion on reduced exposure products.

Some of these products may fit the special rule for marketing modified risk tobacco products, where reduced risk or harm is considered reasonably likely based on the best available scientific evidence without really conducting long-term epidemiology.

Producing harm reduction by reducing exposure to specific harmful substances, follows the well established principle of dose response toxicity. But his straightforward concept for individual substances is confounded by the chemical complexity and interactions in smoke or
tobacco.

Approaches that reduce total smoke exposure, rather than reducing selective substances, may ultimately provide more successful harm reduction opportunities.

These concepts were illustrated by the continuum of risk that we discussed in our December 2009 submission to the Agency and presented to the Tobacco Product Scientific Advisory Committee.

Cigarette smoking is the most hazardous form of tobacco consumption due to the inherent risk of combusting tobacco and inhaling the smoke. Selected constituent reduction is a scientifically valid approach to reducing this harm.

But there's a wide gap in the fundamental understanding relating specific chemical exposure by means of tobacco or smoke with disease outcomes.

To quote the Chair of the Institute of Medicine Committee that produced

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the report, Clearing the Smoke, "there is little direct evidence that removal of specific substances from tobacco smoke or tobacco actually reduces risk or harm to human health.

In considering the health effects of modified tobacco products it is important to remember that the health consequences of the use of any such product are not determined by the toxins that are removed from the product, but by the actual exposure to the toxins that remain."

I'd like to raise two topics that I believe are worthy of discussion today, and these might be more global discussion topics. First, uncertainty is expected in the reduced exposure product review process. Some decisions may require a great deal of scientific judgment when applying the standard of reasonable likelihood. Absolute proof will not always be available.

Second, the reduced exposure

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product review process must accurately balance
the potential benefits of reduced exposure
products with the continued risk of tobacco
product use.

With respect to uncertainty, pre-
market studies have many limitations when it
comes to predicting human population outcomes.
Monitoring changes in health through post-
market studies may take a long time and this
will require patience.

The statutory process for reduced
exposure products accepts uncertainty. While
rigor is necessary, the process should remain
open to reasonable assumptions based on
scientific principles.

Regarding risk benefit, the
process allows for continued tobacco product
exposure. Reduced exposure products will
likely carry their own risks. Although
hopefully considerably less than cigarette
smoking.

The potential benefit of risk
reduction, produced by a reduced exposure product, should not be unnecessarily derailed by the prospect of continued tobacco product exposure.

The modified risk tobacco products provision of the Family Smoking Prevention and Tobacco Control Act is vital to achieving the goal of harm reduction.

Reduced exposure is an important element of this harm reduction goal that should be driven by the concept of reducing cigarette smoke exposure and effectively moving consumers to lower risk products.

I anticipate many diverse opinions during today's discussion. We saw some yesterday, but we also saw a number of agreeable positions. So I'm happy to add my perspective to this workshop.

MR. HOLTZ: Thank you. Our next speaker will be Scott Tomar, D.M.D., M.P.H., doctor of public health as well. He's a professor at the Department of Community
Dentistry and Behavioral Science at the University of Florida College of Dentistry. He's been involved in epidemiological research on tobacco, and smokeless tobacco in particular, for nearly 20 years and has published and lectured widely on the topic.

Dr. Tomar served as a working group member and chair of Exposure Sub-Group for the International Agency for Research on Cancer 2007, Monographs on the evaluation of carcinogenic risk to humans, Volume 89. Smokeless tobacco and some related nitrosamines. He also served as a contributor on six reports of the U.S. Surgeon General on Tobacco.

Dr. Tomar has given invited testimony on smokeless tobacco, including a critical review on the evidence for these products as modified risk tobacco products before the U.S. House of Representatives subcommittee on Commerce Trade and Consumer
Protection.

He serves as a consultant to numerous international, national and state agencies on tobacco issues, including the World Health Organization, the International Agency for Research on Cancer, the U.S. Centers for Disease Control Prevention, National Institutes of Health and the American Dental Association.

Dr. Tomar received his B.A. and D.M.D. degrees from Temple University. And Ph. Degree from Columbia University and Certificate in Dental Public Health and a Doctorate in Public Health degree in oral epidemiology from the University of Michigan.

He is a diplomat of the American Board of Dental Public Health. Dr. Tomar.

DR. TOMAR: Thank you. And thank you for the opportunity to participate in this. First, as a disclosure, I served as an expert witness on behalf of plaintiffs in lawsuits brought against manufacturers of
smokeless tobacco and cigarette products.

So we were given a number of questions we were asked to address in my brief opening remarks. I really wanted to focus on one of those questions, which was Question 3, what scientific evidence would inform a determination of an MRTP as it is actually used by consumers, will expose consumers to the specified reduced level of a substance.

And I think, in particular, I wanted to focus on that. Because a comment that was made by one of the panelists yesterday is that the FDA, its primary mission it to protect public health.

So while there's certainly a need to focus on individual level of risk, we really need to consider how these products are not only intended for use at the individual level but how they're actually used in a population level which can have sometimes an unintended negative impact on public health.

So just a couple principles that I
was going to put out there as part of my
remarks. That several of the speakers
yesterday, several of the panelists as well as
the IOM report on potentially reduced exposure
products, both included that, at least at this
point, the technology is not yet there to be
able to remove a specific chemical, or group
of chemicals, from cigarette smoke.

And the behavior of smoking itself
is also fairly complex behavior. And I would
say that, at least at this point of our
knowledge, both cigarette smoke and smoking
behavior are currently too complex to predict
that we would have a significant reduction in
risk. Either at the individual or population
level from reducing single of few chemicals
from the smoke.

The exposure to many toxins cannot
easily be eliminated in a combustible product.
I mean we already heard for, just an example,
some of the reproductive health effects,
things like carbon monoxide will certainly
always be present in very high levels in any combusted product.

And even if it was technologically possible to develop a reduced risk cigarette, keeping cigarette smokers smoking, rather than quitting, is actually a negative public health outcome.

And several speakers yesterday mentioned the light cigarette debacle. Even if that had been a reduced risk product, which of course it wasn't, but even if it had been the net effect could very well have been extremely negative if it kept people smoking who otherwise would have quit.

So in looking at the non-combustible MRTPs I would hold that dual use with existing products is not likely to produce significant risk reduction.

As was mentioned yesterday the nature of these products if they are developed and marketed specifically to promote dual use, for cigarette smokers to use these as a bridge
product was the term that one of the speakers used yesterday, if they're used as a way for smokers to maintain their smoking when they're faced with increased Clean Indoor Air Laws that is not a public health benefit at all.

And I would add to that that not only is a product being promoted already for dual use, as promoted primarily to young people, and that in fact is the segment of our population which has, in fact, the highest prevalence of dual use.

Is adolescent and young adult males, probably not a surprise because really where these products are largely being targeted.

So to me a non-combustible product that would want to make any claim of being a modified risk product would need to effective in producing a complete long-term smoking cessation.

So it's a product that, when actually used in the population, led to a
measurable and long-term quitting completely from cigarettes.

And in terms of comparing that within the class of non-combustible products I would say that product would also need to be effective in producing complete long-term cessation from the traditional smokeless tobacco products, which, as we already know, have very high levels of known carcinogens and other toxins.

So what do I think we would need? Long-term smoking cessation studies and control studies in which the cessation rate is significantly better than what is already the best available in non-tobacco cessation strategy.

Post-market studies showing that they do not concurrently still smoke or use other conventional products. And post-market surveillance to ensure no initiation by non-users.

Several speakers yesterday
mentioned post-market surveillance. And one
of the things, and I'll put that question out
there and I would hope that at some time
during this discussion we actually include the
other panelists as part of the discussion.

But once we do post-market
surveillance what should be the role of the
FDA. And I put that out there because we have
an example already where we have independent
surveillance from two different surveillance
systems in the United States showing
significant increase in the use of smokeless
tobacco products.

After a decade of decline in both
cigarette and smokeless tobacco consumption
we've now seen three years of up-tick among
high school males in smokeless tobacco use.
And so how does FDA act on that information?

MR. HOLTZ: All right. Thank you
very much. Our last member of the panel is
Jeffrey Willett, PhD. He's a research
scientist with the New York State Department

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of Health and Director of New York's Tobacco Control Program.

In his position Jeffrey is responsible for the development, implementation, evaluation and dissemination of effective tobacco control and public health interventions in New York State.

The New York Tobacco Control Program views tobacco use as a social problem that is best addressed by changing social norms around tobacco use and countering tobacco marketing.

The program recognizes that there is not risk free tobacco product and promotes complete abstinence from cigarettes, other traditional tobacco products and potentially modified risk tobacco products.

Prior to joining the New York Department of Health he served as the director of research and evaluation for the Ohio Tobacco Prevention Foundation. And directed evaluation of and enhanced the strategic
direction for Ohio State Tobacco Control Program.

He served on advisory committees for several national and state tobacco control organizations, including the CDC's Office on Smoking and Health, Legacy and the North American Quitline Consortium.

He has a doctorate in sociology with a focus on the sociology of health and an undergraduate degree in broadcast journalism. Both of them from the University of Nebraska.

DR. WILLETT: Thank you. And thanks again for FDA for inviting the panelists to be able to speak today. In my comments I want to talk about the overall context within which we would be making any determinations of reduced risk or reduced substance exposure.

I believe it's critical to consider the overall context of FDA Regulation around nicotine delivery systems, which include tobacco products, of course, and
marketing.

So Section 907 of the Family Smoking Prevention and Tobacco Control Act authorizes the FDA to require the reduction or elimination of additives, constituents or other components of a tobacco product to protect public health.

We have been talking about Section 911 for the last two days, appropriately, but we can't forget Section 907. The FDA, through this section, can require the reduction but not elimination, of nicotine yields from existing tobacco products.

The construction, components and other properties of tobacco products can also be changed through FDA regulation. So in short, Section 907 authorizes FDA to reduce or eliminate substance exposure for existing product to protect public health.

The authority under Section 907 suggests that any comparison products used for MRTP determinations can be modified to reduce
risk through future tobacco product standards
established by FDA.

One thing we've not discussed or
hasn't even been questioned over the last
couple days is what happens to MRTP
designations when the comparison product
standards are changed through Section 907.

Will we retract those designations
or what will we do to inform the public about
these overall changes and how would we address
those earlier MRTP designations?

Also, as David Burns mentioned
yesterday, the considerations for making
modified risk determinations of reduced risk
are similar to those outlined in Section 907.

The body of evidence that would
lead to an MRTP designation could, and
probably should, lead to an action through
Section 907 to establish overall product
standards based on that body of evidence.

It's also important to look at the
context with regard to nicotine replacement
therapy regulation. And while this is not the role of the Center for Tobacco Products, it is the role of the FDA to regulate nicotine delivery products that make therapeutic claims, such as over the counter NRT. Medicinal nicotine products, such as patches and gum, are safer than cigarettes. And I think all the panelists would agree with that.

However, despite the difference in relative risks associated with NRT use compared to continue cigarette use, Federal policy currently limits the ability of manufacturers of NRT from making direct claims regarding relative risks compared to continued smoking.

Just briefly I want to mention that the New York State Department of Health submitted a citizen petition to FDA requesting that the policies around the control of NRT be changed to increase use of these products that have been determined to be very safe, very

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effective in promoting smoking cessation.

Specifically we've asked the FDA to modify labeling requirements so that the relative risks of NRT use, compared to cigarette use, are clear to consumers.

So of course we're discussing the scientific evidence necessary to establish reduced exposure to harmful substances and tobacco products.

At minimum, the scientific standards to make those determinations should be as rigorous as those required for making any determinations regarding the safest nicotine delivery systems.

And in addition there should be consistent standards across nicotine delivery systems for talking about relative risks. Just briefly I wanted to point to that tobacco product manufacturers are currently able to market their products as alternatives to cigarette use.

These are examples of Camel Snus

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marketing that prevent snus as an alternative to smoking. The ad suggests that snus can be part of a smoke-free lifestyle. These ads ran in New York, in May 2011, around the time that New York City was implementing its smoke-free parks and pedestrian walkways legislation. These ads call on smokers to switch to snus. While, you know, the co-branding and imagery on these ads is concerning these recent campaigns illustrate that non-combustible tobacco products can currently be marketed as alternatives to cigarette use. These ads illustrate how marketing for other tobacco products can support or promote smoking cessation without making relative risk claims or claims of reduced substance exposure. According to the most recent FTC report the tobacco industry roughly $10 billion a year on marketing. There's nothing to prevent the industry from redirecting the
vast majority of its advertising and price
promotions to promote smoke-free products,
non-combustible products, that it believes are
less harmful to combustible products.

So finally, there are concerns
about co-branding that's been mentioned a
number of times over the last couple days.
Dr. McAfee had a slide that illustrated the
percent of youth and young adults who are
smokeless tobacco users who also use
cigarettes.

For the 12 to 17-year-old group it
was about half of those folks who used
smokeless tobacco also smoked cigarettes. And
it was two-thirds, 65 percent, among young
adults. So co-branding is an issue. And when
we're think about MRTP we need to think of the
broader context, conclusive of all FDA
regulation around nicotine delivery systems.

We need to focus on actual product
use. And we need to strongly consider how
these products will be marketed when making
these determinations. Thank you.

MR. HOLTZ: Thank you very much.

I'd like to start off with something that, see if I'm -- We're not here to develop consensus. This workshop is just to elicit opinions and advice and understand the evidence as it exists.

But it sounds like, from this panel, that I'm hearing a consistent message that there is so much uncertainty about the affects of individual constituents of tobacco smoke or any tobacco products.

That there's almost no point in even considering any kind of evaluation of claims that, oh, we can reduce this component.

That the only thing the FDA should consider is a product that says we can reduce all the components? Is that what you're saying?

DR. ALBINO: Really a variation on that theme. We have to be careful we don't get hung up in the trees or the forest. I
mean I think any substance that, you know, we can all identify and reduce in a relatively easy way, in terms of manufacturing and so forth, is fine.

But the real issues is there's very little evidence that we can generate whether that really means anything in terms of health risk. And that's because the complexity. I meant there are examples where, as you remove TSNAs for example, you can increase PAHs and so forth.

So you really have to look at it globally, which is why I was speaking about using very advanced genetics and technology. Where you can get a global readout of what the product is really doing. So you can make a product and reduce whatever you want, but the actual level is really meaningless in a way.

Because no one has a clue to what level you want to take it down to, unless you can take it down to zero. Okay. And many of these substances, I think there's agreement,
while many of them can be reduced, they can't
be reduced to zero, without radically changing
the product.

But I think we can just go right
to the end game and in doing trials you can
really ask the person who is actually smoking
the cigarette what is the genetic, you know,
what's the biological response.

The human cell is the ultimate
computer. And if you get, for example, a
product, and I'm really being hypothetical
here, if you can develop a product, if you
have biological invisibility in terms of
impacts on a lung cell, it doesn't really
matter what's left in that cigarette.

Whatever is left is not clearly
being registered by the cell in any kind of
adverse way. And in that adverse way, the
beauty of modern technology, you can look at
that impact and you can make a direct
relationship to what specific genes or genetic
repertoires or pathways are causal on the
causal pathway to the disease.

So you can take the damage that may or not be there and say, well, the cell is either biologically invisible or the damage produced by an MRTP, for example, is not on the causal pathway.

So I think you can go right to the end game. Modify the cigarette any way you want, but focusing on any specific ingredient and lowering it, I think it's going to waste time and deflect from getting to the end game.

MR. GAWORSKI: So since you started with agreement, I'll agree. I do agree. I don't think you can necessarily take individual constituents off the table. But, as Tony just talked about, it's unlikely, it's a long road.

And the complexity of smoke, all the interactions and, you know, treating smoke as an individual bag of chemicals. Or smoke as a chemical itself are sort of two different concepts.
And it's really a matter of, I think, what's the quickest path to harm reduction. What's the most likely success story that we can have? And you can look at CO. You can look at TSNAs, you can look at PAHs, et cetera, et cetera.

But probably the most successful and the fastest route to this is to get people down that continuum of risk that we've talked about, and others have talked about, to different types of products or products that reduce cigarette smoke exposure, in total.

Rather than in specific substances.

MR. HOLTZ: Yes, Dr. Bloch.

DR. BLOCH: I want to say that I think we need to leave room for the full spectrum of what FDA is likely to want to do. I think in the context of an MRTP a number of people have said, and I think it's probably true, removing one constituent when there are so many others that are harmful is
probably not going to be effective.

But there are some exceptions. I think, for example, nicotine and other things that contribute to addiction, taking those to very low levels at some point may make a very substantive difference.

I think FDA is also obviously considering menthol. Menthol is one which may also thought to be very important to take action on. And there are other things that may fall into that category.

So I think that we just don't know quite, at this point I'm not sure I would make that blanket statement that no single substance or substances is really that critical. That, in fact, may not be the case.

MR. HOLTZ: Just to follow up on the two examples you mentioned. Now, in those am I right in thinking that the main reason that might be good to reduce nicotine or menthol is to reduce the use of the product?

Rather than saying that reducing
that component that you could make a health claim that this is a less hazardous product. But by taking them out it helps people either not start or quit?

DR. BLOCH: Well yes, that's true. A product that isn't used is one that is definitely less hazardous. And FDA has a public health mission and that would seem to me to benefit public health.

MR. HOLTZ: But as far as making a health claim. A reduced nicotine cigarette, would you say that somebody could say that oh, this is a healthier product than, you know, as far as if an applicant comes in and says, hey, we've got a reduced nicotine cigarette.

How in the regulations that will be promulgated about modified risk, how would that be presented in terms of the claims that might be allowed?

DR. BLOCH: Well, I'm not a regulator. I'm a public health scientist.

And I would just reiterate that a healthier
cigarette is one that is less used.

MR. HOLTZ: Okay. Yes.

DR. WILLETT: And again, I think with the nicotine yields, that's something that would be better addressed through Section 907, through Tobacco Product Standards. It's a significant competitive disadvantage for a manufacturer to develop a less addictive tobacco product.

Tobacco products, nicotine is an addictive drug. People want to quit, 50 percent of smokers tried to quit in the last 12 months and were unsuccessful. It's largely, or in part, due to the addictive nature of the product.

So to have a more even, competitive balance I would assume that the FDA would want to use its overall regulatory authority to address nicotine. Similar to the way it's examining the menthol issue.

MR. HOLTZ: Dr. Albino.

DR. ALBINO: I'm glad you brought
that up in terms of nicotine. I'd like to
point out that Vector developed a product
called Quest, it was a series of three
cigarettes with dramatically reduced nicotine,
with the third one being nicotine free,
through genetic engineering.

We approached the FDA in 2004, we
were granted an IND application approval. We
conducted a multi-center, randomized, double-
blind study. And the claim that we wanted to
make was that a nicotine free cigarette, you
know, in the step down unit, would promote
smoking cessation.

We completed the Phase II trial,
we presented the data to the FDA, we were
negotiating to do a Phase III. And the point
being we did do that. We had a clinical
trial, we had an IND from FDA, which is really
a first.

Because the product was focused,
it had a medical claim. And it was a company
that was looking to make a product that could
promote smoking cessation. And it did, the
data showed in the Phase II trial that it was
50 percent better than a nicotine patch by
itself.

So my point being the companies
are willing and able to make these kind of
products. Okay. But there needs to be a
regulatory framework for it.

There needs to be public health
buy-in. So when you mention nicotine, well,
we had a product like that and it promoted
smoking cessation.

DR. WILLETT: And I guess I would
say, you know, there are nicotine products
that are even safer than the products you're
talking about. Over the counter NRT. There
are Federal policies that prohibit NRT from
being sold in every location where tobacco
products can be sold.

In unit sizes that can be
competitively priced with cigarettes. So we
have to look at everything. We cannot have a
regulatory system that disadvantages the most
safe form of nicotine use, or places barriers
around the use of the safest form of nicotine.

And allow tobacco product
manufacturers to control the retail
environment where those products are currently
being sold without having a more even handed
approach with NRT.

DR. TOMAR: You know I just wanted
to come back to a point that Dr. Burns had
made yesterday. That when you have a car with
an exploding gas tank, well then you take that
off the market and you go with a car that's
not going to explode.

So if the technology exists to
create a cigarette that would lead people to
quit, which as we've said, is really the only
safe cigarette is the one that's not smoked.

Then I think it would be, I think
the FDA would have a public health mandate to
then set a product standard to create
cigarettes that will no longer addict the next
MR. HOLTZ: Yes.

MR. GAWORSKI: You know, I appreciate the comments around the product standards. But you know we're sort of talking about reduced exposure in this context. So I want to go back to the retail comment that you made.

And sort of think about the future and what the whole statute sort of brings up in terms of retailing and structure around that.

I mean there is a structure around that, that FDA will control in terms of marketing new products and how they're communicated and what we say and how that's done.

So I think we do have to sort of separate the past from the future in that context.

MR. HOLTZ: Yes. And please introduce yourself for the recording.
DR. SHIFFMAN: Saul Shiffman, from the University of Pittsburgh. I want to build on what Michele said about one of the ways to reduce the harm from smoking products is to have people use less of them, that the safest cigarette is the one that's not smoked.

And to connect it to some of what Scott said. Now Scott framed the issue in terms of smokeless and safer products and NRT leading to complete cessation of use of smoking products, and that's clearly the ideal.

But the point I'd like to make is that there's likely utility from products that would reduce people's use. Even if they don't eliminate the use of smoking products. That if those were reduced it's likely that there could be some benefit in terms of harm reduction.

So we've talked about dual use as though it's inherently harmful or has no potential for harm reduction. But I think
we're talking about that in a context where
you leave smoking untouched and now add
smokeless products, for example, in situations
where smoking is prohibited.

But I think what we need to look
at is the possibility that smokeless products
could be used by an individual who continues
to smoke, but by the use of smokeless
products, NRT, reduces his or her use of
smoking products temporarily or perhaps
permanently continues to smoke some.

And that that's an avenue to harm
reduction that we ought to keep on the table
and not be too absolute about complete switch,
even if that's the ideal. That I think there
could be some benefit from smoking reduction.

MR. HOLTZ: I'll let Dr. McAfee
make a brief comment, but still do want to
give the majority of the time to the panel -

DR. MCAFEE: Yes, just a quick
nuance or caveat around that. The 2010
Surgeon General's report emphasized that we
have more evidence around the harm from
duration of smoking than we do around the
intensity of smoking.

And I think, again, this is an
area where there's two populations and, as
Michele pointed out, it's very different to
think if, say you had a 18-year-old who used
smokeless, who smoked a cigarette twice a
month or something and that was stable for the
rest of their life.

We don't know if that's even
possible or if that's what would happen. But
that's very different from a 50-year-old who
has got a 50 pack-year history and they switch
over to smokeless and cut their smoking in
half, I think we're pretty clear that that's
close to nil in terms of a public health
benefit.

And we need to be very, very
careful about any claims or any misdirections
of it. So I don't disagree conceptually, but
I think we need to keep those caveats in mind.
MR. HOLTZ: Let's go back to, Dr. Tomar, what do you think? Because you mentioned in your presentation that you don't want to see products out there that would actually end up helping people maintain their smoking or other tobacco use. Where they're just switching to these other products because of clean indoor air laws and other related issues.

DR. TOMAR: Well, and again, I think the point was made by several speakers yesterday. It's not just the characteristics of that product, but how it's marketed and to whom it's marketed. What we're seeing now in the products already on the market, so clearly there are smoke-free messages from some of the products.

And we saw some of the examples of those ads. But there are also, there's a whole other line of marketing material for that same product for Camel snus, clearly
aimed at young people. That's the market segment that they're targeting.

As has been said several times, that's the segment of the market that has the highest prevalence of dual use. So a product that's keeping them both as smokers and users of other products I don't see as a public health benefit.

Actually Dr. McAfee made the point that exactly I was going to make, that even reducing from a pack a day to half a pack a day after you've been smoking for 20 years, it's probably not a measurable reduction in risk. Certainly not substantial if that's what the FDA's intention is.

MR. HOLTZ: Yes.

DR. BLOCH: Yes, I'd like to piggy-back that on to say, I mean we've spent, the community has spent 20 or 30 years enacting, importantly, clean indoor air laws which are now in effect in about half our states.
And in addition to protecting non-smokers, they've had a tremendous impact on changing social norms and helping drive smoking rates down. And also probably encouraging people to ban smoking in their own homes.

So this is a very significant issue if smokeless tobacco, if advertising and marketing for smokeless tobacco, as was shown by our colleague from New York State, and that kind of advertising is not that new.

It's been around for awhile and it's clearly aimed at sustaining smoking in smoke free environments and that's a public health negative.

MR. HOLTZ: Yes.

MR. GAWORSKI: So I'll just bring up the issue of dual use one more time. There was a paper that actually we published last year, or the beginning of this year if somebody wants to go through PubMed, or they contact me for dual use, or that citation.
But it looked back at about, I think there was 17 or 19 publications in the literature that we found around dual use. And I appreciate the comments around when you quit or when you smoke and the impact on that.

What that literature told us, or indicated, and this is the current literature at least. Is that, in terms of smokeless tobacco, risk is really driven by that cigarette smoking habit.

So if you reduce your cigarette consumption, again sort of that total smoke exposure concept, you don't really add that much risk in terms of smokeless tobacco use, in terms of dual use.

And, in fact, you will have transition of people that will go to total smokeless use. You will have people that quit tobacco altogether.

And you will have people that continue to smoke. But directionally all those things sort of take you down that
continuum of risk.

And I guess, you know, I
appreciate the comment about people, you know,
that maybe have longer pack-years or whatever,
but we still have to think about those people
in terms of how we can help and then what we
can do for that population.

MR. HOLTZ: Just to get some
detail on what you just said. How much of a
reduction should the FDA consider to be a
threshold.

You know, what would be
substantial or important if somebody wants to
make a health claims that, oh, use these snus
or whatever other product in order to reduce
your smoking.

How much reduction would they need
to show happens in the real world before it
matters? And then what kind of standards
would you think would be needed to be applied
to say how do you show that it's not
maintaining a habit and dissuading people from
quitting entirely?

MR. GAWORSKI: Well I think, again, those are sort of wrapped in those surveillance issues. And how much is an interesting question.

I'm looking at my colleague out here for the one paper, Gottfredson I think it is that shows a 50 percent reduction in smoking you get something like a 25 or 30 percent decrease in lung cancer risk.

So it's not a 1:1 type comparison, you know, we see that a lot with cigarette smoking, it's not a 1:1 correlation. But directionally it's a benefit. And to the extent that it helps people move down that continuum, I mean that's the benefit.

And you'd look for that, I think, in whatever pre-market studies you could do. But honestly a lot of that is going to be sort of epidemiology after the fact.

MR. HOLTZ: What do you the rest of you think? Is there some sort of a number,
you know, whatever the number might be, where
you could say that reducing cigarette smoking
by this much could be considered a health
benefit if you switch to smokeless?

And how do you then factor in
maintenance rather than quitting?

DR. BLOCH: Well I just want to
reiterate something that Dr. McAfee said,
which is that duration is a far, far more
important determinate of risk than is amount.
Amount, particularly with cancers, rises
linearly, but with duration rises
exponentially.

And one of the things I don't
think we've done as good a job as we can with
tobacco users is explaining to them that it's
not enough to quit. Rather, it's important to
quit as early in life as possible.

Because the earlier in life you
quit the less likely you are to suffer from
tobacco related illnesses. And for me,
there's going to need to be a very high
threshold to show that, for MRTP products, that they are not interfering with what we need people to do, which is to quit.

MR. HOLTZ: I have another question here, in the second row. And again, please introduce yourself for the record.

DR. BORGERDING: Mike Borgerding from R.J. Reynolds Tobacco Company. It's been very interesting listening to the panelists. If I didn't know better I'd think this was perhaps a panel around risk or performance standards.

I haven't heard a lot of comments about reduced exposure. In terms of reduced exposure the Act indicates that, of course, there have to be studies to make sure that a consumer wouldn't perceive that there's been any demonstration of reduced risk per se already.

There are obviously toxicants in cigarette smoke that have been identified and we can do measurements to determine that
there's been reductions in exposure with
different products.

There's quantitative risk
assessment available to look at the net of
what happens and, while I take all the
comments as quite important, I haven't heard
a lot of discussion about what would define a
reduced exposure product and what should be
done to consider these in the marketplace.

MR. HOLTZ: Thank you.

DR. SHIELDS: I just want to make
a couple of comments --

MR. HOLTZ: Again, introduce
yourself for the record.

DR. SHIELDS: Peter Shields, from
Georgetown University, but next week it will
be Ohio State University. So I don't even
know what to say any more, that's not natural.

So there's a couple of things,
first of all, in terms of reduction in smoking
and reduction of risk, right now we're still
guessing.
Okay, and risk, you know, we won't really know and so we're going to have to model now, and those models will still be, hopefully informed guesses, okay.

In terms of smoking reduction, those studies are doable. Okay, now we have a very hard time doing those studies because we can't find those people who switch to snus, or try snus.

The tobacco companies know who they are, you know, they send them the coupons, they got the mailing lists. They know who are smokers, who are now using the coupons for snus and so they could be tracked.

And we could probably find that answer, at least short term use what's happening to smoking over a couple of years. And that's an answerable question.

In terms if reduction of risk, I mean, since we don't know that dose response curve looks like in general. Let alone the reverse dose response curves.
We're not going to know whether or not a 25 percent reduction in smoking really is going to decrease risk. There's some evidence that there's a benefit from those, you know, northern European studies. But those are not great studies and no-one's going to rest on two studies.

You know, that would be really dangerous. Basically all over again like what was going on with the light cigarette story.

So we have to remember that if you're a smoker and you reduce your risk, okay, the only known way to do that is to quit.

And at any age you quit you do get some benefit from it, okay. But the older you are the less benefits you're going to get. So if you go down from a pack a day to three quarters of a pack a day, we're guessing, but that doesn't sound like that's a whole lot of progress.

And if these are people who might
have quit then there's harm there. And so we need, you know, we can do those studies. You know it's not that hard to answer as long as we know who those people are and the various test markets for RJR who is selling the stuff across the country.

You know, they could be done, but we have to remember that smoking one cigarette a day does increase risk, there's evidence for that. And environmental tobacco smoking increases the risk of lung cancer, okay, so any amount of exposure to smoke is still going to be bad.

So the question is is how many people are going to be hurt versus helped. And that's something that we're ultimately going to have to guess at long term.

MR. HOLTZ: Dr. Albino, as we were just hearing something about, if we're looking at exposure and you start saying that the things that are doable.

And that sounded a little bit
different than some people were thinking, gosh
there is so much we don't know, is it even,
these biomarkers, what do they mean?

Can you tell me a little bit more
about what is doable in terms of trying
especially, you know, a shorter time frame?
Figuring out whether these changes have any
help to outcome the effects.

DR. ALBINO: Right, I think one
way to do it is to be able to parse the
various types of damage into what's on the
causal pathway, what's not on the causal
pathway. And it's being done in oncology
across the board and I'll just give you one
example.

For example my home institution,
former one, at Sloan-Kettering, every lung
cancer is sequenced for ten or 15 genes, and
these genes are driver genes, okay? And if
they're mutations, they're immediately
reflexed to a therapy that going to deal with
that mutation, regardless of the type of tumor
it is or anything else.

The point is if the driving mutation, if you impact that gene you can get a regression. And you can get a response. It's the same thing with the kind of damage we're looking for.

You can have a product, and you can look at the kind of damage you get. Let's take smokers right, you know, chronic smokers, advanced smokers. Fifteen percent get lung cancer, you know, 30/40 pack a year and 85 percent don't.

One question is well if that 85 live long enough, you know, 120 years would they eventually get a lung cancer, okay.

We'll leave that on the side for now.

But at the moment we can measure, you can measure the kind of damage that you see in the smokers that get lung cancer. You can measure the kind of damage in high risk smokers, who at high risk might have symptoms, they might have an imaging issue.
There are genetic signatures out there. You can do a bronchoscopy and you'd say, these people do not have lung cancer and they're at low risk for acquiring lung cancer, despite the fact that there's plenty of genetic damage there and there's other gene signatures that can look on a smoker and say, these two bronchoscopies, one definitely has lung cancer, you know, so the imaging may be real.

And one the imaging, you might have a nodule there but it's not lung cancer. So what does that tell you?

It tells you that the genetics and the sophisticated technologies are good enough to predict risk of lung cancer in an advanced smoker with a lot of damage already to feel the effects in various types of damage caused by smoking.

But it's not the right damage.

What we're really learning in oncology is that it's not the damage per se, it's the right
kind of damage.

And half the audience out here I'm willing to bet cause I see a lot of grey hairs, are harboring some kind of pre malignant or malignant disease. They will die with it not from it, because those malignancies do not have the right kind of damage.

We see a lot indolent cancers of lung and prostate and colon and breast, it's a real eye opener. So there's indolent cancers right. Why are they indolent? They don't have the right genetic damage, they don't have the right driver genes.

So you can look at that and say here's an advanced smoker and predict who's going to get lung cancer and who's not. But that tells you if you back off, it tells you the kind of damage which is on the causal pathway and the kind of damage that's not on the causal pathway.

With that you could backtrack, in
my opinion, and develop products looking at those kind of signatures. I mean, it's obviously going to be much work, but the technology is there to be able to replicate, you know, an impact and exposure with the causal pathway. Which is what we really need to know. It's much more important than knowing whether the product is reducing the substance. Might be irrelevant.

But if that substance, if we can cause show causal pathway or not causal pathway, then we have a better biological rational for saying this product has a better chance of reducing risk of disease than this product.

MR. HOLTZ: Let's see, do we have another, yes, Mr. Shiffman. Please keep it very brief so, because I know I've got questions for the panel.

DR. SHIFFMAN: Let me keep it brief, and this is going to bring us back to the issue of dual use and reduction or
cessation of smoking.

I'm not aware of solid data on this for smokeless tobacco products but there are solid data for nicotine replacement products. That when you engage smokers who are not interested in quitting at baseline and dual use.

That not only does it not impede cessation, but there are now multiple studies showing that it promotes cessation. So one of the, and I don't know that that's -- how much that's about the product versus being the kind of framing of the use, how it's marketed.

But we ought to consider that sometimes, and in these studies, again, I want to emphasis people were screened in on the basis of saying they're not going to quit.

That engaging them in a dual use paradigm, in this case with medicinal NRT products, actually led to greater cessation.

So we can think of that as the extreme of harm reduction, if you will,
through the introduction of oral nicotine products.

MR. HOLTZ: Dr. Block, you mentioned that you've done a lot of work in terms of reproductive age women and the effect on pregnancies, and early development.

As some sort of system is set up here should there be some, if you find that there is a group in the population where there is a particular health risk.

Should there be some sort of threshold there saying that population must be protected. And if it doesn't protect population then even if you say oh, you know, men might benefit but, you know, we can't do it.

We need to veto it because of these developmental problems that are related to fetuses. Particularly you mentioned nicotine, where we've heard a lot of discussions say, oh if we can just get people to switch to tobacco derived products that
give them their nicotine, then we've made
great progress.

But you're saying, well, those
developing fetuses might still be at risk.

DR. BLOCH: Well, I think it's an
important point and I think that one of the
key points in my presentation is that the
population of smokers is quite diverse, they
are old, they are young, they are healthy,
they are non healthy.

It's noteworthy that many of our
studies screen out the elderly, those who are
not healthy, woman who are expecting to become
pregnant. And so those populations who are
likely to be at increased risks aren't --
don't tend to be, you know, don't tend to be
part of the risk equation.

And I think we do have to give a
lot of thought to how to deal with these
diverse populations. Including the large
number of women who are tobacco users and who
are going to potentially use MRTP products.
And one point I would make, and I made this point in my presentation is, you know, most people who smoke want to quit and that especially true of women when they become pregnant.

Their intense desire to quit makes them very, very vulnerable, smokers are looking for reassurance, most of them know at some level, although they don't really understand the health risk, but they have some sense that smoking's not good for them and the people around them and they should quit.

And they've generally tried and they haven't succeeded and they know that it's not easy and they're not sure that they can make it happen. And so they are looking for reassurance, and I think the key thing here is not to give them false reassurance. Not to reassure them when that is really not the right thing to do.

MR. HOLTZ: Does that bring up, it seems to be a related point to the overall
strategy in these modified risk tobacco
products.

And when you try to push for
abstinence or cessation being the number one
thing, and when you just try to reduce harm.
We've heard analogies to condoms for reducing
the spread of sexually transmitted diseases or
clean needle exchanges.

And that those are examples where
people are being harmed by the existing
circumstances out there. And here is
something that can reduce their harm and that
that's considered a good public health
measure.

But in this case, you know, what
do you think of those analogies does that
apply in this case or do you need to insist
that these products lead toward less total use
and ultimate cessation and not initiation?

DR. BLOCH: Well, I think there
are many different opinions on that subject
but I think the overarching goal for FDA is to
think about population harm because that's what really matters.

DR. WILLETT: I can provide my perspective as a public health practitioner. There are at least two and a half million smokers in New York state.

Most of them want to quit, many of them have tried to quit, so part of my role is to help inform the public about tobacco use and the importance of quitting.

The importance of improving the health of people who currently smoke, which the most effective way to do that is to quit. So we cannot give false reassurance to tobacco users.

We also cannot create a completely muddled picture for the public health community that is making progress reducing tobacco use and reducing the harms caused by combustible tobacco use primarily.

So my perspective is, an MRTP designation that is not based on the most
robust standards that clearly indicate reduced population harm is going to counter ongoing effective public health interventions and the net is a loss in that scenario.

MR. HOLTZ: So this panel is about exposure, does it matter then, would you even entertain a claim that a product reduces exposure of any or all components if it doesn't also lead to reduced use?

DR. WILLETT: Well, I'm not sure it's only about exposure. Don't the considerations include the likelihood that it would reduce harm? Would reduce the overall morbidity and mortality, you know, to individual tobacco users.

So that is part of this, it's not just solely an exposure or substance issue, it's also the likelihood that there will be reduced harm -

MR. HOLTZ: Then to pin you down, again. So if an applicant came and said this product reduces exposure and we're not going
to make further claims than that, would you
even say there's any value in entertaining
such a limited claim?

DR. BLOCH: There would be no
value for me, as the director of a tobacco
control program. Unless there was a
relationship, clear scientific data support
from FDA that this was reducing harm, across
the population, I would do nothing with that
information.

DR. ALBINO: And I agree, more
importantly, it would have no value to the
consumer or to the industry. Making a reduced
exposure claim, would have no impact on the
consumer.

So it's not in anyone's interest,
including the industry's interest to go, it's
all about harm reduction. I mean, I think you
have to look at the historical data, I mean,
there have been multiple products introduced,
Eclipse, Accord, you know we had a Quest, our
nicotine free cigarette.
These all had either, you know, direct claims or inadvertent or implied health claims, these were all products that failed in the marketplace.

They failed because the consumer does not respond to any kind of reduction claim or any kind of health claim or anything like that from the industry.

And so under the FDA now, that it would have the imprimatur you I know it's imprimatur would impact the consumer. Reducing exposure, if that lead to reduced risk then the FDA would adjudicate that, then that's something else.

But just saying, you know, we have 50 percent less of something, would be of no value to anyone.

DR. BLOCH: Could I comment on that?

MR. HOLTZ: Yes.

DR. BLOCH: I think that's right, I think that on the one hand, to go back to
something Dr. Shields said yesterday, reduced
exposure ought to be helpful even though we
don't know that it is.

And so if we can reduce exposure
we should and that of course was the impetus
behind the TobReg proposal that Dr. Burns and
others did, but the question then is what to
communicate to the consumer.

And I think there's every reason
to be very concerned about communicating a
reduced exposure claim to consumers who are
vulnerable, who are looking for reassurance.

And who are, not unreasonably,
would think reduced exposure would mean
reduced risk, because they're not in general
sophisticated scientists.

And we can't tell them that
reduced exposure, at least in today's world,
we can't tell them reduced exposure implies
reduced risk. So I think that reducing
exposure is a good thing, but communicating it
to the public is probably not.
And I actually think, and I would ask Dr. Burns to comment on this, that that was a point that the TobReg group specifically made.

That government should mandate reduced exposure but they should also not permit those claims, or pardon me, that information to be conveyed to the public.

MR. HOLTZ: And Dr. Burns.

DR. BURNS: Let the record reflect that I was asked to do this. You're absolutely correct, we did that, in the context of cigarettes where it's very clear at this point in the science that the kinds of reductions that were achievable couldn't be quantified as meaningful in terms of health.

We've also done the same thing for smokeless where, at least in my view of that evidence, is very clear that geographic differences that have led to profound differences in disease outcomes are almost certainly related to differences in exposure
from the products used.

So we need to be a little bit cautious about throwing exposure completely over the side, because at least for smokeless tobacco products it would appear that there's compelling evidence that decreases in exposure do indeed lead to meaningful differences in disease outcomes.

MR. HOLTZ: Mr. Gaworski.

MR. GAWORSKI: I guess I was just going to follow up. One of the unique aspects, I guess, of at least the reduced exposure 911(g)(2) is all you can really communicate is the reduction of some substance or elimination of some substance.

And actually I think in the statute you have to test the meaning of those communications to people. So there is some requirement that the manufacturer test that in the population or in a sample.

To say well, what to people take home from this message? Again the statute
sort of covers that communication aspect and if it's false or misleading then you shouldn't be saying that.

MR. HOLTZ: What is that, what's your sense of what you would need to see in focus groups or other testing?

Would you need to see that virtually everyone understands that there's no health claims and is that even possible? I mean, it just seems like the natural human reaction is if you say you reduce a toxic product that people are going to say, oh it must be healthier then. Can you possibly make an exposure claim without implying some harm reduction?

MR. GAWORSKI: It's intuitively very difficult, yes, I would agree with that but, you know, it's still a possibility.

DR. BORGERDING: Again since the purpose here is to share ideas I'll offer a differing opinion from the moral analysts. I think there is value in having products that
have reduced exposure.

I believe that such products are not intended to communicate reduced risks. They are intended to communicate the facts of reduced exposure.

The challenge indeed is to make sure that those communications are not construed as indicating that reduced has been demonstrated.

An additional challenge is to make sure that the science is there to support the likelihood that there is a reduction in morbidity and mortality.

And we do have a responsibility, in my opinion, to communicate information like that when it is scientifically demonstrated, and I think there is value in that.

MR. HOLTZ: Dr. Tomar.

DR. TOMAR: There was a point that I think was made yesterday, and I'd like to reiterate.

That if, in fact, the technology
is available to R.J. Reynolds, to Altria, to
other companies that are now, and I'll use the
smokeless tobacco example because that was the
one that was just raised.

If, in fact, the technology is
available to substantially reduce the exposure
to a specific class of carcinogens in those
products. Then I think rather than allowing
those companies to use that as a marketing
advantage for one specific product that they
make. I think that the FDA then has a public
health mandate to require those manufactures
to use that lower level for all the products
in that product category.

MR. HOLTZ: Yes. Dr. Albino.

DR. ALBINO: First of all the FDA
does have the power to lower substance and so
forth. Again it's missing the forest for the
trees, without reduced risk you could actually
make a product worse.

You have to be very careful, this
is an extremely complex product. Once you
light the cigarette you have hundreds of
thousands of chemicals moving around in
milliseconds.

You have to be, just reducing
substances is not really, I think it's
problematic, without coupling it to reduced
harm you could be going in the wrong
direction.

And, you know, I think the FDA
realizes this and certainly the companies
realize this. This is why we're all
working toward, and while almost all the
panels, regardless of what they started with
all come back down to the same thing, reduced
harm.

Because everything funnels into
that. Without reduced harm everything else is
not irrelevant of course, it's meaningful, but
to what end, and we need to know what that end
is.

And the communication, again in my
opinion, can only be to the consumer can only
be driven by the FDA.

And I'll just give our Quest example, we had a nicotine, it was nicotine free it wasn't by smoke dilution or anything, it was genetically engineered.

It has as much nicotine as the nicotine control patch in the nicotine patch trials. It had zero nicotine. And yet, we were accused of making an implied health claim and we said well it has no nicotine that's an analytical fact.

But later surveys showed that 50 percent of smokers think their nicotine causes cancer. So they said well it has no nicotine it must not cause cancer.

So, you know, removing nicotine is what is in the end is everyone's, you know, dream child. We did it, we couldn't market the product, we had no buy in. The consumer misunderstood the product, the FDA though, the FDA said, it wouldn't allow the cigarette was nicotine free to make a medical claim the
consumer wouldn't have the right information at the right time and would believe the FDA not the company.

But they would have to inform people that nicotine does not cause cancer. So you know there's a lot of misinformation out there, through no fault of the companies themselves, right, this is just misinformation.

And so we need someone to kind of package all that and put it in the right framework, educate the consumer and allow the companies to make a true claim that does not get misread by public health or by the consumer.

MR. HOLTZ: Dr. Tomar.

DR. TOMAR: And I absolutely agree with everything you've said. Which is why I said with the combusted product, I honestly don't think that technology is there to be able to remove any -- and I understand the caveat about, you know, potentially -- the
exception being -- things to make the product more attractive or more addictive.

But in terms of the other chemicals I don't think we have the technology to remove or lower any specific one. And be able to know reliably we've actually reduced harm and we may have actually increased it.

And it's why I think with the combusted products, I honestly don't think that we're ready for any reduced risk claims for any combusted product.

But in terms of non combusted products, and I assume that what Dr. Burns was referring to was much lower levels of tobacco specific nitrosamines in Swedish types of snus compared to conventional U.S. types of smokeless tobacco.

And I as thinking now that the companies that control almost the entire U.S. market for smokeless tobacco products make products both with much lower levels of TSNA as well as products that still have very high
levels.

I think that that speaks to the FDA being able to require, the technology is available, to reduce their entire product category of smokeless tobacco products to the lowest possible level that's technologically achievable.

MR. HOLTZ: And specifically this question came up yesterday about getting into something that is similar to substantial equivalents.

How if you want to say, consider the Swedish experience, but this is a product made by a different company in a different plant how -- what kind of information would you want to see to say, yes, there is a good chance that maybe this would be the kind of product that might get the health outcomes that we saw in Scandinavia?

DR. TOMAR: Well, the Swedish experience I think is somewhat of a misrepresented case study but I didn't want to
Because in fact, that we've seen a tremendous decline in smoking among women who in fact have not adopted snus to any large extent. And they've had an almost parallel decline in smoking.

But in terms of, there are a number of studies that, yes, IARC has in fact concluded that several of the TSNA's that are found in high concentrations of smokeless tobacco up to NNN and NNK, are carcinogens.

If the technology is available to reduce that then that should be done. I don't know the advantage of allowing a company to manufacture a products with lower levels of these carcinogens and higher levels and then allow them to use that as some kind of market advantage.

Oh, our product is less likely to give you cancer than this one, why not just require the manufacturers to manufacture it to the lowest possible level that's achievable,
of these known carcinogens.

MR. HOLTZ: There were comments yesterday about public, what the speaker said was public misunderstanding, of the risk of snus or other smokeless tobacco products.

That there was a perception that they were as bad a cigarettes and that was a failure of communication by everyone involved.

What do you think about that, should the FDA allow this class of products that are non combustible to say we're better than cigarettes?

DR. TOMAR: You know, while on the one hand your studies have been done among smokers have in fact found that substantial portions perceive comparable risks from smoking and using smokeless tobacco.

Well, a big part of that is actually a misperception of the degree of risk to which their currently at from their smoking.

So while they don't perceive a
difference in risk it's mostly because they
tremendously underestimate their personal risk
from their current behavior of cigarette
smoking.

So I think that, you know, if
there was only a matter of telling the public
that something is dangerous, I mean the first
Surgeon General's report came out in what,
1964 and here we are with 20 percent of adults
smoking.

So obviously education is
important but it's not the entire answer to
it. Do I think we need a better job of
communication? Absolutely, and I'm looking
forward to hearing from the perception panel
later today. I think that's a huge challenge.

But I don't think that that's the
entire answer. Oh, if we would just tell
smokers this is, you know, this is less
hazardous, don't they all flock to it? I
think that's very simplistic.

MR. HOLTZ: Mr. Gaworski's been
MR. GAWORSKI: Well, I was just going to suggest, again, we've sort of wandered into product standard territory, which is probably another workshop later downstream somewhere.

But I did want to get back to the special populations, I think that's sort of an interesting topic to poke at. I think all of us have struggled with how to do that or how best to do that.

There's certainly some limitations and some hesitancy I think that people feel about. Well, I mean, can you actually go ask pregnant women to use a tobacco product, how do you do that? The word ethics came up yesterday. What are the right, how do you do that with structure?

And I would suggest to the FDA that, you know, when they think about guidance or whatever that's a very serious discussion, I think, needs to have some time spent on it.
And some, you know, work together, I guess, to figure out how do we do that, and what are the controls. Is it appropriate for the industry to do that, is it somebody else? How is that done?

MR. HOLTZ: Dr. Willet.

DR. WILLETT: Communication is key, communication to specific sub populations, pregnant women, youth, African-American community, around menthol.

I mean communication is critical, and to look at the combustible versus non combustible communication in a different way. Rather than looking at it as an allowance for certain products that say we're safer than.

There is a stronger message that cigarettes, combustible tobacco products are much more dangerous for you. I think that sends a completely different message, people wouldn't necessarily flock as much to the other products as they would have a stronger motivation to quit.
I'm not saying that's an approach I advocate but when you look at communication you need to look at both perspectives.

And if you say something is less harmful it's going to promote the use of that product. And from a public health standpoint, promoting the use of a product that has known risks is problematic from an ethical standpoint for public health practitioners.

MR. HOLTZ: We're coming towards the end of this session, so if there are any, anything that we haven't covered that we should have or summary statements you'd like to make, Dr. Albino?

DR. ALBINO: Sure, just briefly, just a follow up on that last comment. All I think reduced risk products, I mean what's the operative word in that, risk. It's a fault the products are still going to maintain and have some risk.

But the risk of maintaining this status quo is the worst outcome, the worst
possible scenario. All these products will lead more or less to reduced risk, I mean, smokeless, MRTP's

It's the question of how their introduced, how their marketed, and what kind of claims are made and what kind of emphasis is placed on it by the public health community and the FDA.

I mean if it's real consensus around that, we can lower the risk, and it's not really for this panel to do decide, it should be zero risk everyone should move off cigarettes, I mean people shouldn't smoke, obviously.

But we have 75, you know, 40, 45 million smokers, 45 million ex smokers who are at risk for reuptake again. The risk of keeping the status quo is the worst thing we can do. And we need to move down this pathway where ever it leads.

MR. HOLTZ: Dr. Bloch.

DR. BLOCH: Well, I thank again,
FDA for convening the panel and I would say again that we have to consider the diversity of tobacco users.

And while I would just comment, because I've heard this come up on a number of panels that you know we're, where we are now, you know, we can only move in a better direction.

I would point out that the future is uncertain, and it is possible to make things worse. And think that the number one goal and it's going to be medical nostrum of, first do no harm. Don't make things worse, and you can do that.

MR. HOLTZ: Mr. Gaworski.

MR. GAWORSKI: I would also like to thank the FDA for this workshop and allowing us to participate. I think the last two days that I've sat here, again, we have a number of different opinions but there's a great deal of agreement, I think, between a number of people here.
Which is encouraging because I think the modified risk process is the future and, you know, we look forward to more engagements of this type. So, thank you.

MR. HOLTZ: Dr. Tomar.

DR. TOMAR: Just a reminder, the most effective means of reduction of exposure is reduction in the use of these products. Quite frankly, if we weren't seeing a decline in per capita cigarette smoking I'm not sure that the major manufactures that are here would have invested so heavily in non-combustible tobacco products.

It is now they can control almost the entire U.S. smokeless tobacco market and sometimes, yes, we have a long way to go.

We still have obviously many more smokers than we should but things, in some cases we forget that we've actually been making progress.

We do have some tobacco control approaches that are effective. And I just
hope that we keep that in mind as we move forward on developing so called less harmful products.

MR. HOLTZ: Dr. Willett.

DR. WILLETT: And one thing I've heard a lot over the last couple days is the risk of doing nothing.

If we do nothing within this specific provision of the Tobacco Control Act, we're doing harm or we're not doing anything. That is completely untrue and if you look at the Tobacco Control Act as a whole, I think the areas that have the greatest potential to reduce harm and improve public health were the advertising restrictions, that were to go into effect.

You know black and white text only advertising, restrictions in outdoor advertising. The graphic health warnings which, you know, there's recent litigation over the graphic health warnings.

They're provisions of the Tobacco
Control Act that will have tremendous public benefit. The tobacco industry is fighting those. Disagreement over whether this little sliver of the act around modified risk tobacco products will have public health benefit.

And it all comes down to demonstrating that there will be reduced harm and clearly communicating what that means to the public in a way that actually does reduce harm. Thanks.

MR. HOLTZ: Thank you, that's a great segue to our next panel on consumer perceptions. Thank you very much, to this panel. So we'll now take about a 15 minute break, I've got five after ten, so let's try to be back here at 10:20.

(Whereupon, the foregoing matter went off the record at 10:06 a.m. and resumed at 10:24 a.m.)

MR. HOLTZ: One thing I neglected to do in trying to get started again this morning, was to reintroduce myself. I'm Neal R. Gross & Co., Inc. 202-234-4433
Andrew Holtz.

I am an independent journalist, so nothing I say in any way reflects FDA policy or anybody else's. I'm just asking questions here.

And don't read anything into the tone of my questions or what I'm saying, because the point really is to elicit the conversation, not to imply any conclusions about who's right or who's wrong.

Now we're finally getting to a panel that we've nibbling at since the workshop started, consumer perceptions of modified risk tobacco products.

Because as we've seen from the oft-referenced example with light cigarettes, you can do anything you want with the product but it's how you used and what people believe that is really critical to what happens in the real world. So it's great to get into this discussion now.

Our first panelist is Lois Biener

Neal R. Gross & Co., Inc. 202-234-4433
Ph.D. She's a senior research fellow at the Center for Survey Research, and adjunct professor of psychology at the University of Massachusetts Boston.

She's been involved in research evaluating tobacco control interventions for over 20 years.

She's served on federal advisory panels for major tobacco control interventions in the United States, and has provided expert assistance to the state programs in Massachusetts, California, Maine, New York and Wisconsin.

Much of her research and writing has focused on the impact of pro- and anti-tobacco media and marketing, on perceptions of tobacco products and on smoking behavior in adults and youth.

Her work was one of the original investigations to isolate and discuss the importance of emotional content as a factor contributing to the effectiveness of anti-
tobacco television advertisements.

Dr. Biener has particular expertise in the design and implementation of population surveys. Most recently, Dr. Biener has been studying population response to new modified risk tobacco products both combustible and noncombustible.

Her research has focused on developing measures of awareness in use, receptivity towards these products, assessing perceptions of harmfulness and responding to corrective information regarding knowledge of regular health risk.

She is currently carrying out an NCI-funded population based survey of receptivity to new snus products in Indianapolis and the Dallas-Fort Worth area.

Dr. Biener holds a doctorate in social psychology from Columbia University.

Dr. Biener?

DR. BIENER: Thank you very much.

And I'm happy to be here and finally have an
opportunity to really focus on consumer perception.

Focusing on the question that we were given, which is, you know, what evidence do we need to be able to determine that consumers will not be misled, I also want to also emphasize that we're talking now about pre-market research to provide this evidence because the next panel will be discussing post market surveillance.

So the question is, what can we do before these products are actually out on the streets generally, to know that consumers are not being misled by representation that this product either does or does not contain particular products and does or does not reduce risk?

And I believe that from the evidence that I've been collecting over the past few years that it is possible after exposure to appropriate educational messages, consumers should be able to differentiate
between reductions in toxic constituents
versus reductions in associated health risks,
because that's the state of our knowledge.
And we also need to make sure that consumers
can appreciate the existing gaps that there
are in scientific knowledge. And I don't know
whether you can actually, maybe you can see
this box.

The health information box that I
just put up on the screen is part of a study
that my colleagues and I did when we were
investigating perceptions of Advance and
Eclipse that were on the market, a combustible
product.

There was concern that these
products were seen as being, you know, as
entailing less health risk. And the question
here was, is there something that we could put
up, some kind of message that we could give
consumers that would clarify what we did and
didn't know about these products?

So what we did was simply use the
Advance and Eclipse ads, and for half the group we put this health information on the ad and for the other half we didn't. And this was a door-to-door survey among low-income neighborhoods around Boston.

And we had people look at the ad. We also showed them a graph that showed the differences in three major toxicants in the products that showed that these new products were much lower than the standard light cigarette.

And then had them read the health information box which said you may or may not experience a reduction in toxins, this one was for Advance, if you switch to Advance from a very low-tar cigarette, if you puff more deeply or more often with Advance than with your current cigarette, or if you smoke more Advance per day than you are now smoking.

And Advance may not reduce your risk of lung disease because it's not known whether the amount of reduction is large.
enough, et cetera, you can see what is on the box.

The results showed that the presence of this box compared to people who saw an ad without the box reduced the consumers' likelihood to perceive a reduced health risk from this product.

And the presence of the box did not have an impact on their perceptions of differences in toxicity because that was demonstrated to them in the graph that showed the reduction in toxicity.

So this was a very minimal exposure to corrective information and not particularly skillfully done the way advertisers are able to do that.

And so what that said to us was that it's possible for consumers to be informed. And I think we need to also keep in mind, I just want to make a few more points, that what are our goals in communication and labeling policy?
And those goals are first of all to reduce tobacco related morbidity and mortality, and to do that what we need to do is to increase smoking cessation and reduce smoking initiation. So that's what we need to keep in mind.

We also have to provide accurate and relevant information to consumers so that we support choices that will reduce risks and support trust of health agency messages. To not do that I think really undermines the health agency.

And we have to keep in mind that there is already misperception out there related to anti-tobacco messaging, and that misperception is that most smokers believe that smokeless tobacco is as harmful as cigarettes.

And the possible consequences of this misperception are that there is probably a reluctance to switch from cigarettes to smokeless tobacco since they're perceived to
be equally harmful.

    So I will leave it at that.

MR. HOLTZ: Great, thank you. Our next panelist is Monica Graves, M.B.A. She is Director Regulatory Oversight at R.J. Reynolds Tobacco Company, where she leads the development and execution of all regulatory related behavioral research and population level post market surveillance studies in anticipation of potential FDA requirements for certain tobacco products manufactured and distributed by Reynolds American, Inc.'s tobacco operating companies.

    Specifically Ms. Graves' focus has been on developing and executing both pre-market and post market research to support new and modified risk tobacco product applications under Sections 910 and 911 of the Tobacco Control Act and the related population health standard requirements.

MS. GRAVES: Thank you, Andrew.
Today, after yesterday, I have to say it seems as if there's general consensus in terms of the opportunity that modified risk products present in terms of improving public health, or at least a consistent level of interest in pursuing the potential and learning and figuring out what the potential is.

So there is a common place to begin in terms of looking at the opportunity to lower population levels of disease.

And specifically in doing this, it means that we would be providing adult tobacco users of higher risk or higher exposure products who do not intend to quit or will not quit, with the option to use reduced risk or reduced exposure products.

But at the same time, limiting those unintended consequences is equally as important. And this requires that we communicate clearly above and beyond those products that exist today in the marketplace, what impact modified risk tobacco products
would have in terms of slowing the rate of cessation that would otherwise exist.

So basically we have to look at the population level impact as well as the individual impact, and what impact if any a modified risk tobacco product would have beyond those rates that occur in the marketplace without a modified risk product in there.

So minimizing unintended consequences requires clear communications regarding what we do know about the reduced exposure or the modified risk product as well as what we don't know about the reduced exposure or modified risk product.

(Off the record comments.)

Specifically, what we believe the statutes provide for in terms of clear communication as it relates to reduced exposure products is that reduced exposure does not mean reduced risk.

And in terms of modified risk
tobacco products, we believe that the statutes are providing for clarity of message in terms of reduced risk does not mean no risk.

And we, in fact, agree that that clarity of message for those two pathways of products is absolutely critical to minimize the unintended consequences.

Pre-market research should focus on clarity of message. In all the marketing materials and labeling for risk perceptions the message for reduced exposure products is, clarity of message is looked at in terms of what do they perceive the message to mean? For reduced risk information, clarity of message is, do they comprehend what we're saying about the risk?

These evaluations can be made pre-market as Dr. Biener indicated, so for this panel we are addressing the scientific evidence on a pre-market basis.

The statutes lay out two learning objectives in terms of the scientific evidence
pre-market. The first one is, will consumers be misled by representations about reduced exposure products?

And the second one is, will consumers have an accurate understanding of the risk associated with modified risk tobacco products?

So moving back up to misleading, concerns that representations would be misleading, the recommended methodology that we've kind of been exploring and would love to talk here today about is a, what we refer to as a perception study.

We would advocate that it's a web based survey to assess, quite frankly, how consumers interpret the information about reduced harm or reduced exposure products.

In terms of after being exposed to the proposed labeling and advertising, does the language mislead and what are the consumer take-aways after being exposed to the advertising and labeling?
A couple of study design points, interpretation of marketing materials occur in the context of a consumer's personal experiences, constructs and histories.

And for a perception study, we believe it's critical that you would have a control sale to identify the noise that occurs outside of what the communication materials are.

In terms of will consumers have an accurate understanding of what a modified risk communication message is, that study would be similar, in our mind a web based survey, but focusing on consumer understanding of the risk communication as presented again in the proposed labeling and advertising.

Quite simply this would be, do the consumers understand the language in the materials? A study design points here minimal exclusions.

Obviously you want to represent comprehension among the majority of the
population, and then of course basic literary
skills should be considered as you design your
materials in the study. Okay.

All right, just to summarize here.

And I was hoping actually that with such a
short CV I could take up the extra time in my
presentation. So I apologize.

MR. HOLTZ: Well, be sure to get
to your points.

MS. GRAVES: Okay, basically the
three things that I believe would really
benefit all of us to have a discussion about
today, first and foremost, is who's the
consumer in these provisions?

And, you know, if they refer to
consumers, in our view that's an adult tobacco
customer. That's the way we interpret these
provisions.

If the FDA has a different
interpretation in terms of what the consumer
is and the audience that would need to be
studied, the FDA must clearly communicate that
through regulation or guidance that that is
the audience that needs to be studied, because
it is our policy that we do not study and
historically haven't, consumers beyond adult
tobacco consumers.

Two other points for us to talk
about would be the acceptable target levels.
When we design the studies, what are the
acceptable target levels for perception and
comprehension studies?

Setting overly burdensome
thresholds for consumer perception or
comprehension levels run counter to the
statutes and FDA stated objective to reduce
the health consequences of tobacco, overstate
the importance of perceptions versus actual
behaviors in the marketplace, and also ignore
the imperfect nature of messaging, which we
know even perfect communication is not always
understood.

And then the other area to explore
is when we look at these two questions and
scientific evidence, are we literally looking at clarity of message in terms of reduced exposure meaning not reduced risk takeaway from the consumer?

And in terms of reduced risk products, is the clarity of message an objective that the consumer clearly understand that reduced risk does not mean no risk?

MR. HOLTZ: Thank you. Our next panelist is Manoj Hastak. He's a professor in the Department of Marketing at the Kogod School of Business American University in Washington, D.C.

He holds a Ph.D. in business administration from the Pennsylvania State University.

He's served as a consultant on consumer information processing, advertising communication, deceptive advertising and labeling, and research methodology issues for several federal agencies including the Federal Trade Commission, the U.S. Department of Justice, the Food and Drug Administration, the Department of Housing and Urban Development, and the Bureau of Alcohol, Tobacco and Firearms.

Dr. Hastak?

DR. HASTAK: Thank you very much for inviting me to be a part of this workshop. Just a brief introduction about myself, since I believe I'm a little bit different from the other panelists here at the table and in this workshop, primarily because I don't specifically work on tobacco related issues.

My research is more broadly focused on advertising and labeling communication issues.
And specifically for relevance to today's panel, I work on deceptive advertising issues, you know, detecting deception, and I also work on disclosure.

And I should also say that I've done a fair amount of work with the Federal Trade Commission on these issues, and I'll be talking about some of those studies and interesting findings.

And a quick disclaimer on that is that I don't certainly speak for the FTC or for any of its staff. So here we go.

I wanted to talk about a couple of things and then hopefully get into them in more detail later on.

The first issue is tied to the question that was posed to us which is, you know, what scientific evidence is needed to show that advertising for MRTPs is both truthful and non-misleading, that it doesn't create false take-aways or beliefs from consumers?
And the two previous panelists have talked about this to some extent. In fact, Monica, I think laid out a study in some detail, a web based study. And I kind of echo those sentiments.

The point I would make here quickly is that you need consumer research in the form of controlled experiments. In marketing we call that copytesting.

And the idea is to compare advertising or other promotional materials with control materials. This could either be a cleansed ad or a different control ad.

And again we can talk about that in more detail to more precisely assess the takeaway that consumers have from the advertising.

And the other related issue that I think we should talk about is what the dependent measures in these consumer perception studies or copytesting studies should be.
And by the way, the approach that I’m talking about here is one that’s been used a lot at the FTC. In deceptive advertising cases it’s a well-recognized methodology. It’s been litigated in court several times, so it’s kind of a worthwhile approach to look at.

And in terms of dependent measures, you know, looking at either pure takeaway, you know, what is it that people think the ad or the label is saying or suggesting to them versus impact type measures whether they be on consumer beliefs or behavioral intent, which is beginning to get at materiality issues, you know, is this issue important to consumers?

The second issue I want to talk about is that, you know, if there is evidence that shows that these ads are misleading that, you know, people take away the claim not only that this product is low in some toxic substance, but that the product is safer that it’s better for your health, then one option
to try and correct that misperception is to use a disclosure, and that's an area in which I've done a lot of work.

And I just wanted to raise some challenges that one would face in developing and testing a disclosure in this particular area.

One of the problems with these kinds of disclosures is that they're often interpreted by consumers as legal disclaimers as opposed to substantive disclaimers.

A classic example in my mind would be, I don't mean to pick on the FDA here but the FDA disclosure that comes with let's say dietary supplements that says something like, these statements have not been evaluated by the FDA. This product is not intended to treat or cure a disease.

And if you think about that statement for a moment, you know, do you process that as a substantive informative disclosure, or do you see that as a legal
disclaimer and what does that mean? And we can talk about that in more detail.

The second point I'd like to make is that disclosures that are seen as contradicting the main claims in an advertising or on a packaging are often doomed to failure when you compare that with disclaimers that are qualifying a claim.

And an example from some work I've done in weight loss would be that if an ad says you can lose 50 pounds using this product and the disclaimer says the product only works if you diet and exercise, that's a modifying disclaimer. It's qualifying the claim.

But if the disclaimer says there is no scientific evidence to show that the product works, as a consumer that's a contradicting disclaimer.

It's difficult as a consumer for me to know what to do with this, because the advertising says the product works, and you tell me there's no scientific evidence that
the product works.

Both statements may be true, or one or both may be untrue, but it's a difficult situation for the consumer to deal with. And again, I'll talk a little bit more about that later on.

Disclosures that contradict a name, a brand name, are inherently problematic. And again I notice I'm out of time here, but one quick example here from an FTC matter.

A weight loss product called Fat Trapper that basically, extensively said the product traps fat, and had nice visuals to show you how it does that so the product is very effective.

If you cleanse this ad of all weight loss claims and put a disclaimer that says the product doesn't reduce weight, but the name is Fat Trapper, you can figure out how the consumers might interpret this. It's not an easy thing to interpret.
And I'll leave the last thing for further discussion. So let me stop there and I look forward to an interesting exchange with the panelists. Thank you.

MR. HOLTZ: Thank you. Our next speaker is Pam Ling. She's an associate professor of medicine at the University of California San Francisco where she conducts research on tobacco media and social marketing to young people.

Her work includes analyses of thousands of previously secret tobacco industry documents detailing marketing strategies targeting young adults.

Dr. Ling has special interest in young adult tobacco use and counter engineering tobacco industry marketing, the global proliferation of U.S. tobacco marketing strategies, marketing to women, smokeless tobacco marketing and using market research to guide clinical and public health interventions.
Dr. Ling's clinical work is in general internal medicine. She has special interest in caring for under served urban populations.

Dr. Ling received her bachelors degree from Harvard-Radcliffe in history and science, and her M.D. from the UCSF School of Medicine.

She completed her residency in internal medicine at the UCSF San Francisco General Hospital primary care program where she emphasized adolescence and AIDS clinical care.

She received her masters degree in public health from UC Berkeley.

Dr. Ling?

DR. LING: Thank you. I also want to thank the FDA for the opportunity to participate in this interesting workshop.

So when we talk about modified risk, we cannot consider the MRTP in isolation. The risk is always compared to
some standard which is usually the conventional cigarette.

However, it's well documented in the scientific literature that smokers underestimate the risk of smoking, and that these misperceptions are associated with reduced intention to quit.

So we cannot accurately communicate modified risk without correcting the communication of the risks of smoking. This is a challenge because smokers have been systematically misled for decades about the risks of smoking with, for example, as been raised previously the example of light and low tar advertising.

These misperceptions are likely to continue, because even with the elimination of the terms light and mild from advertising, tobacco companies have already responded with color coding for consumers telling them how light is now gold, and have produced packages for retailers telling them how to substitute...
color coded packs for the old packs.

    So this is an example of the consumer education about switching lights to gold, and here's the retailer material telling retailers how to switch the gold packs for the light packs.

    The discussion so far has really focused on some quantitative testing for perceptions of consumer risk.

    And I did want to raise that qualitative testing also provides rich information on how consumers interpret risk information and how they transmit it to others.

    This is particularly important as viral word-of-mouth marketing, social media, blogs, message boards and testimonials are increasingly used in the marketing mix.

    This was the case with the product Eclipse, for which Dr. Shields showed us the product information yesterday. This is a little bit of consumer perception data on
Eclipse.

And I have an example here of a focus group that was done with female smokers in Atlanta where they showed them this chart illustrating the smoke composition.

And then if you hear the conversation that goes on later when they ask the smokers, how would you describe this product to a friend at home?

They quickly translate the graph of 80 percent to mean that the product is less harmful. This happens quite easily for consumers.

So this kind of qualitative data may not end up in the top line summary of the focus groups, and because of that FDA should request that all pre-market qualitative testing be made available for review independently.

In addition, quantitative tests are needed that exceed simple tests of whether consumers understand or can identify a basic
message.

The tests should include estimates of perceived risk, risk reduction or selecting the product that's safer, similar to the trials that have been to test warning labels and plain packaging in the literature.

As others have mentioned, model the population risk and how they're affected by consumer behavior including tobacco product initiation, smoking cessation, relapse, dual or poly tobacco use, are as important complement to the individual risk perception data.

Accurate communication of modified risk must be linked to clear communication of conventional product risk.

Because the affected populations are disproportionately low literacy and lower SES, clear, graphic and easily understood communications are particularly important.

I don't know that we have any communication right now that's been as kind of
capturing the imagination about the risk of
smoking as well as the Pinto with the engine
that blows up that's been already mentioned
yesterday.

Similarly, to avoid misleading
consumers into believing that the conventional
products also have reduced risk, MRTP products
should not be marketed as line extensions of
existing brands.

So if you believe an MRTP is safer
and is branded with Marlboro, you may end up
believing that all Marlboro products are
safer, erroneously.

Similarly, sellers should provide
this quantitative and qualitative data to FDA
pre-market. These kinds of studies have been
conducted extensively before the marketing of
cigarettes.

However, since the tobacco
companies' prior expertise has been in
misleading the public, the data should be
independently reviewed and validated.
Finally, post market surveillance should be accompanied by enforceable pre-market agreements to immediately withdraw new products if data suggests consumer risk perception is happening leading to adverse population effects on MRTP or conventional product use.

MR. HOLTZ: Thank you very much.

And our final panelist in this session is Saul Shiffman Ph.D. He's a research professor of psychology, psychiatry, pharmaceutical sciences and translational clinical research at the University of Pittsburgh.

His training is in clinical and health psychology, and he has studied smoking and smoking cessation for over 35 years.

His work has included studies of smoker perceptions of light cigarettes, and of tobacco products claiming reduced exposure or reduced risk.

He has also studied the beliefs and behavior of lights smokers and written
about the potential population effects of
tobacco products claiming reduced risk.

He's also studied risk perceptions
of medicinal nicotine products as well as
clinical trials of their efficacy and safety.

Through Pinney Associates, Dr. Shiffman consults to GlaxoSmithKline consumer
health care, which markets smoking cessation
medications, and has an interest in a company
developing new medications for tobacco
dependents.

Dr. Shiffman?

DR. SHIFFMAN: Let me start with a
little bit of an introduction, and really it
follows from what other panelists have already
laid down.

We've heard over the last day and
a half, some panelists talk about just putting
information out there, just giving consumers
accurate information. And unfortunately it's
not that simple.

Communication is the act of
transmission of information from one party to be received by the other, and so what matters is not what is put out but what is actually received.

Just the phrase has already been used that it's the consumer takeaway from the information not the content of the information itself that's crucial, and as you've already heard that's actually embodied in advertising law.

So lawsuits under the Lanham Act which prohibits false advertising rely entirely on what the audience takes away not what the manufacturer actually puts out there. And that introduces the complications we're dealing with today.

Let me show you some examples. Let's have the first slide, please.

So this is some of the material that was put out for Eclipse, and what you see there is the literal wording of some of the claim, which essentially was an exposure
reduction claim, although you can see that it starts to go towards harm reduction and it mentions illnesses but doesn't explicitly promise reduction in illness.

So that's the message on the communicator side. Let's look at data to see what the consumer takeaway was.

This shows the amount of risk reduction, disease reduction, the amount of reduction in risk that a sample of current smokers and ex-smokers perceive.

So what you see is that essentially 75 percent of smokers thought that it reduced risk of disease by at least 50 percent.

And maybe more unexpectedly, about 25 percent of both current and ex-smokers thought that these cigarettes would be completely safe. That we had eliminated 100 percent of the risk.

So this illustrates the disconnect between the explicit message on the one hand
and the consumer takeaway on the other.

And going to what FDA needs to do,
and I think we've heard consensus on this, is
not just look at the content of the message
but actually have empirical data about what
the audience takes away.

So let me show you some other ways
in which consumers interpret information in
surprising ways.

So we found in a study about
people who smoke so-called light cigarettes
that the biggest correlate of their belief
that these cigarettes were safe was not any
information, any explicit sort of scientific
quantitative information about delivery, but
rather their sensations that these cigarettes
seemed less harsh to them.

So think about it. If you're a
consumer, who are you going to believe, FDA
giving you some numbers or the evidence of
your own senses? If it feels lighter and less
harsh it must be less harmful.
And this is not something that the tobacco industry was unaware of. If you look particularly back in time, a lot of claims which really I think were meant to be health claims were really about irritation, not so harsh on your throat, which you naturally I think want to interpret as meaning that the products are safer.

And as you've already seen, even color can communicate something. So in another study, folks at Roswell compared two packs of Marlboros that were identical that neither one contained delivery information, neither one contained safety information. There were no claims, that they weren't labeled as light, they differed only in color. But in fact, 53 percent thought that the gold pack had to be lower in risk, whereas only eight percent designated the red pack.

Obviously the remainder was sensible and thought they were equal. And 31 percent actually thought that cigarettes that
came in a gold pack would magically be easier
to quit.

So the point is that again we not
only need to look at consumer takeaway, but
consumer takeaway in response to a variety of
inputs not just the text messages and explicit
info.

So some issues and challenges,
what is it that you test? All of the tests
we've seen including the ones I've just showed
you are really very poor representation of
what happens in the marketplace, because in
the marketplace the consumer isn't looking at
a single claim.

They're not just looking at the
pack. They're surrounded by PR information,
by buzz, by talk on the web and so on.

So I think it's important that we
actually get beyond these very isolated tests
where you're looking at a piece of
information, to look at the whole brand
positioning, a really 360 degree review,
because those other elements can have a big
effect.

Similarly, in such copytests
they're really artificial because you have a
single, very brief exposure and that's not
what happens in the marketplace.

A brand establishes itself and
it's identity over time, and so we need to
look at methods that give you a chance to
examine that.

One of the things we talked about
yesterday was the idea of using market tests,
test markets to evaluate these, and I think
those have the opportunity to present a more
realistic view of how a brand creates
perceptions.

I think we need clearly to test
smokers and ex-smokers and I believe that we
need to test these in youth. If we're
concerned about these products enhancing
initiation, we need to look at populations
that are vulnerable to initiation which
includes people who are not adults.

We've talked about testing
takeaway beliefs, and actually the issue was
introduced about what the standard should be.

So I mentioned that there's a long
record in FTC in that Lanham Act litigation of
these. And in those, the courts have ruled
that if as little as 10 or 15 percent of
consumers are misled, the message in the
advertising is considered misleading.

So if that's the standard for
misleading advertising about dish soap, what
should be the standard for misleading
advertising about a life or death matter? It
should clearly be rather stringent.

So it's not good enough if, for
example, the majority of smokers take away the
right message. To be accurate it really needs
to not be misleading even to a small
proportion.

And finally, I just want to note
that these studies are loaded with what in

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behavioral science we call demand characteristics, which is that the consumers are pretty smart and they know that the right answer is to say oh yeah, I don't believe that reduces my risk.

We need to push past that with methods that look at kind of true underlying beliefs, and there a message such as implicit attitude tests that are validated to capture that.

We may not want to get into that discussion now, but the point is to really get a very sensitive read on real takeaway. Thank you.

MR. HOLTZ: Thank you. One of the many questions here that comes up is, exactly if in the pre-market time frame what exactly do you think the FDA needs to require?

Is it, as we heard from Ms. Graves, some testing of perceptions and understanding? Or does there actually have to be, all the way to the other end, test
marketing where you test not just intent to behave but actual behaviors in a test environment?

What kinds of standards do you think the FDA should require of an applicant?

DR. SHIFFMAN: Yes, I think that if one does it in the context of test marketing rather than an isolated copytest that I think it might be unrealistic to expect to look for actual differences, for example, in quitting that would take a long time to develop.

But we do have proxy measures of intention to quit one could study, whereas normally if you're doing a test market for the purpose of evaluating the market potential of your product you're just really asking, how many people want to buy my product and who are they?

But in this case we might want to ask, what is the effect on the people who are even not buying the product? Are people
buying the product who are not in our public health target?

For example, people who have already quit but come back into the tobacco market to use the product. So I think it's feasible to get some initial proxy measures of that in a test marketing context.

DR. HASTAK: Yes, I would I mean first of all, I agree with Dr. Shiffman's comments in general.

I think doing longer term studies even if you're focusing just on consumer perceptions and not behaviors, looking at the impact of these advertising materials on beliefs when there is repetition, people are exposed to them over time, is important.

But it strikes me that there are also practical issues here in terms of what kinds of research is available before a decision can be made as to whether certain claims should be allowed and what kind of disclaimers are permissible on them.
So to some extent I think you may have to rely more on the kind of methodology that you see in Lanham Act cases, for example, or in FTC advertising cases, perhaps with a greater focus on beliefs than on advertising takeaway.

I mean and I think again Dr. Shiffman is right. I think, you know, a single exposure isn't the ideal situation within which to do this kind of testing, but some of these methodologies have been developed to the point where one can get reliable readings, early readings, even in the face of the kinds of demand characteristics that you talked about. So I'm sort of agreeing with him, but it strikes me that there are methodologies that are used elsewhere to decide if advertising is truthful and non-misleading or if disclosures are being effective.

That doesn't stop I think the responsibility of the FDA or the manufacturers...
from collecting data over time to demonstrate that there aren't these long term kind of lingering beliefs or long term belief impact issues. So that would be my position.

MR. HOLTZ: Dr. Biener?

DR. BIENER: I think that when it comes to consumer perceptions of tobacco products that we really need to think much more broadly than simply what the manufacturer is going to do in order to advertise their product.

I think that what we really need is an intensive public education campaign on the meaning of these modified risk products. And within that campaign would come a more intensive understanding of what are the components, what are the constituents in tobacco that are really dangerous?

And we've done a lot of that with dietary information. There's been a lot of dietary information that's gone out to the public in terms of fats, saturated fats,
carbohydrates.

I think that the public needs this kind of information about what is the meaning of nicotine and nicotine levels? What are carcinogens in tobacco? What's the difference between combustible and non-combustible tobacco?

And I don't think that we can rely on tobacco companies to do this. I think that our health agencies need to put out this kind of information so that we start to inform the public.

And another point I wanted to make that may not be related to your question is that in order for us to decide what the standard is of, you know, this is accurate perception, the FDA really needs to set out, what should be the content of the information?

What is accurate and what is inaccurate? Because there's not really agreement.

There's disagreement within the
community and certainly disagreement between tobacco control, I think, folks in the agencies, tobacco control agencies and scientists.

And I think that that needs to be clarified and FDA is going to have to take a stand on that.

MR. HOLTZ: Ms. Graves?

MS. GRAVES: In response to your question in terms of what evaluations should occur pre-market, I believe that there are two areas to explore. One is clarity of message.

And based on the statutory requirements or expectations in terms of comprehension or perceptions, standards need to be established around that built into your study design, your success measures and so forth, and executed.

I believe qualitative is part of that process. Not so much in terms of that being information to inform and be provided to the FDA as far as scientific evidence, but can
be very beneficial in terms of understanding what consumers, where they might be getting confused.

Or what is it about a particular word choice or diagram or something that's in the communication that seems to be taking them off?

So I see value in that as well as making sure that as you develop your questionnaire you understand what the question means to them.

For example, the statutes use language like less harmful and less risk of disease.

And so one thing you'd want to evaluate in your qualitative is, do consumers understand the difference between those two terms, such that if they appeared in a questionnaire would they see a distinction or would they think this is a trick question, what's going on? This means this and so forth.
So I do agree that there's value in qualitative in terms of being able to improve clarity of message and provide that instate that you want in terms of clear comprehension and perception.

So qualitative preceding a quantitative assessment of clarity of message in terms of what's perceived, if it's a reduced exposure or what's interpreted, or understood if it's a comprehension type test for reduced risk.

The other evaluation that I believe is important on a pre-market basis is some ability to predict a consumer's likelihood of purchase.

To be able to look at relative interest among current, former or never tobacco users just to validate that the intended audience, which is current adult tobacco users, is the audience that is most interested and believes based on seeing the materials that they will or will not try it.
That survey data can be strengthened in terms of a probability model that could be developed.

We've done some work and believe that consumers in general, not necessarily just in tobacco, but in general do pretty well at predicting their behavior for trial.

And I'd be interested if any of the other panel members have experience with someone's ability to say, you know, I see this ad and I see what this product's about and, you know, on a scale of one to ten I'm going to try it or I probably wouldn't try it. So from that experience you can build an algorithm.

So you can take any potential modified risk or reduced exposure product to a consumer group, current, former, never tobacco users, and expose them to the marketing materials.

And then with a validated algorithm based on what they report their
level of interest is, you cannot only get relative appeal, is it primarily appealing to the audience based on their survey results.

But you can also overlay that with an adjustment factor developed from the algorithm that then takes what they say they will do to what they actually will do.

Because we all know there's a difference between what consumers say and what they do, and also a difference between what consumers perceive and how that might necessarily lead to the behavior that we would or wouldn't expect.

So I think it's important to look pre-market at making sure that there's a clear communication of what we do and do not know about these products as well as trying to gauge relative appeal and try to evaluate the, there doesn't seem to be any major red flags going on pre-market in terms of who's primarily interested in trying this particular product.
Post market is where you get the real data on usage and behaviors, and that's where the evidence has to come from in terms of monitoring very closely, are we at a net benefit or a net harm with this product in the population?

MR. HOLTZ: In your opening statement you mentioned that the -- it shouldn't be overly burdensome. What would be the kind of pre-market test that you would see as overly burdensome?

MS. GRAVES: Well, I didn't mean that relative to the test, but the targets that you would establish in the study design, or the standards that the FDA would regulate or suggest in guidance in terms of, just think of in terms of what percent of your study group did indeed comprehend accurately or did not misperceive what you wanted them to perceive.

I think there's a, I don't know what the answer is. I would just caution that
again it's the post market that is going to inform the true assessment of net population harm or benefit.

And that pre-market should not be overly relied on in terms of the consumer and the behavior aspect of it, because it is not a hard science unlike the evaluation of the claims if you will on the product side.

That it's almost like a red flag, a disaster check, but monitored extremely close in the market in terms of what's going on with behavior.

There's many approaches to how you could establish the standards on a pre-market basis, what percent of this study group is going to accurately respond or perceive accurately?

You could use an FTC claim guideline. You could use, you know, what's precedence in litigation in terms of misleading, on copyright infringement, stuff like that. I think that's 20 percent.
I would actually advocate a sliding scale depending on the benefit. How much risk are you willing to take on the areas of concern?

And it might even be that there's a breakeven. If there's some sort of modeling going on maybe there's a breakeven point at which you could say, you know, if your interest or your likelihood that a nonsmoker or somebody that is trying to quit is overly interested in this product, you know, that there could be a threshold that is evaluated relative to what it would take to flip that equation to a net harm versus a net benefit.

And then that threshold be evaluated against what you see in the study results.

MR. HOLTZ: Well, first, Dr. Ling, did you have a --

DR. LING: Yes, I was a little bit confused by that. I just wanted to bring up this idea of, on just the audience message
testing.

I agree with Dr. Shiffman that it's important to do testing not only in what you say is the intended audience of the message but also to think about these other, you know, audiences that are going to be exposed to the message when it's, you know, when it's in the market, so particularly youth, particularly former smokers.

And even to also to think when you talk about saying you intend to reach current adult tobacco users that, you know, this is not a model at the group.

And, you know, the group that's interested in quitting is maybe different from the group that never intends to quit. And the messages tend to be framed as for those who never intend to quit.

But, you know, the interest among those groups may be different. I'll stop there for now but there was one other thing.

MR. HOLTZ: All right. Dr.
Shiffman.

DR. SHIFFMAN: Let me actually start by building on that. I do think from a public health point of view, the way that we frame the issue is that we would like to see these products most adopted by people who don't intend to quit, because the ones who intend to quit have a chance of getting the best harm reduction which is quitting completely.

The paradox is in every study we've done, the greatest appeal is to people who are interested in quitting, because they're the ones who are even examining their use so they're more interested in and receptive to a message about some behavior change even if it's switching to a lower risk product.

So I think that's, and I agree with your point that we need to segment the audience and we need to be thinking about, how is it having different effects?
And a particular challenge is that the people who are not interested in quitting are hard to get interested in changing products as well.

I wanted to also agree that one can measure intended use. It's standard stuff in market research that you evaluate the potential of your product by looking at purchase intent.

And I think we have a lot to learn from the marketing expertise within the tobacco industry and within industry and companies in general, but it is striking that companies don't actually rely just on stated purchase interest.

Tobacco companies and others do test market. And the reason is that it's one thing to get a stated purchase intent and it's another to see if people actually buy it.

So I think even pre-market there's a role for going from stated intent to observing behavior, and again it's standard
pre-market marketing practice which is to do
a test market.

MR. HOLTZ: So any standard that
the, application process that the FDA puts out
you would tend to favor something that says,
as a matter of course you want to see some
test marketing so that you can see the whole
package, see how it actually, which would then
include the price, the color, the labeling,
the product placement and all of those things
that can get you closer to the real world?

DR. SHIFFMAN: Yes, I think that
would be a more robust evaluation. And as we
mentioned yesterday, there is a potential to
have control markets.

As someone rightly brought up, you
can't contain the message, but you can look at
a market in which the product's not available
in order to get rid of that noise that exists
in any consumer response.

MR. HOLTZ: Okay. One of the
other panelists wants to jump in here. Okay.
And please identify yourself for the record.

MS. SNEEGAS: Karla Sneegas, with the National Tobacco Control Network, and Indiana State Health Department.

I just want to really encourage and urge the Center for Tobacco Products to mandate that youth be considered in any kind of message testing.

They may not be the intended audience as Dr. Ling said, but they are the audience. They are the ones that frequent where these products are placed for consumer purchasing.

They are a great percentage of the audience that goes into convenience stores, for example, and sees these products. And it's just absolutely vital that they be included. That we see how any of these messages are being absorbed by them.

We know from decades of research that the brain is not developed until well
into the age 25, and how youth incorporate the
message they see is very different from how
the adult intended audience may do that.

And it's just absolutely vital
that youth be studied against these messages.

Thank you.

MR. HOLTZ: Dr. Shields?

DR. SHIELDS: Hi, I'm Peter Shields. I've got a couple of comments from
what I'm understanding is the RJR, R.J. Reynolds position here.

So first I would hope that the
standards for the pre-market testing for the
consumer perception is not limited to just web
based testing, okay?

I mean that's to me is extremely
minimal. That's useful, but that's the
easiest and cheapest thing to do and this is
too important to limit it to just that single
methodology.

The second thing is in the concept
that well, you know, we really can't predict
well for the post, you know, what's going to happen post market so we just want to rely on the post market.

Well, you know, what do we want to do, count the bodies after the fact? I mean that would be like saying from the risk perception and the biomarkers and the toxicity, well, this stuff's not really predictable and only a long term epidemiology could tell, so let's just put the product on the market and see how many people die, then we'll know in 20 years.

I mean we have to do the best we can pre-market to identify how people will respond to that product and the marketing of that product.

And the post market is to validate your predictions not to say later, you know, oh okay, so we got it wrong. Let's just do corrective action.

And we touched on that yesterday, today it's more, but corrective action is
always bad. You know, we have to do our best to get it right and we have a responsibility to get it right.

MS. GRAVES: Can I just respond?

That absolutely is not what we are suggesting the weight that a post market would carry. Pre-market is an opportunity to evaluate what you believe is going to occur using not just perceptions as a proxy, but as an opportunity to identify where there are still concerns.

But if you evaluate the interest in the product in terms of people saying that they would try it and then being able to actually predict that level of trial among these audiences, then you do go into post market to validate that.

And again those levels would have to be acceptable. In terms of perception's the same thing, you go in there.

The point about post market is, it's not what people perceive, it is what they do that creates a net harm or a net
benefit scenario.

And it's not a post market plan that you would wake up 20 or 30 years later looking at that then go uh-oh. This is focused on behaviors, behaviors.

And there are ways to do post market studies and post market surveillance to see red flags in the behaviors.

And again you can track perceptions as well, but the real critical information in terms of did we make the right decision pre-market, is what is happening to prevalence that might be driven negatively by this modified risk product.

Does this particular product's user profile source brand new initiatives differently than other products that are in the market?

Does the user profile of this modified risk tobacco product, when you take into account former users of that product, does it have a different quit rate than other
products in the market?

All of those are things that you can look at that are true actual behavior in the marketplace as early indicators that yes, we made a good decision to go out there.

And not just tracking disease state, long term mortality and morbidity, but what's happening with behaviors.

And I can honestly say that we at the same time could feel confident that we're not going to have unintended consequences pre-market that could literally evaluate, or materialize longer term as you get marketplace momentum, perceptions of the particular brand, consumers talking about how they feel when they use the product and so forth.

So it's not necessarily a way to just safeguard against what we think might happen, but also to, you know, understand what actually does happen in terms of it going either way.

MR. HOLTZ: Dr. Shiffman?
DR. SHIFFMAN: Well, I agree that there's some things that are hard to predict and there are dynamics you get to observe and observe on a sufficient scale only post market.

So we want to think about the pre-marketing activities as the best we can do for proxies within a more limited context. Again I'm cognizant that companies do test markets before they go full out.

They're mitigating their risk of investing in something that's not going to work. We want to mitigate our risk of going out with something that's not going to work for public health.

And I think it's a worthwhile analogy to think about drug development and pre-market testing versus post market.

So certainly in terms of safety you start with animal models, then when if that's looking good you start with humans on a small scale and then you test with humans on
a large scale.

We've learned the hard way that even large clinical trials don't always predict faithfully what will happen when a drug is out, but it's our burden and our duty to do the best that we possibly can to test on a reasonable scale to try to predict those things.

So we do large efficacy and safety trials before it's in market and we continue to monitor once a drug's in the market.

MR. HOLTZ: Dr. Biener? Thank you.

DR. BIENER: Well, I was just reflecting on this concern about what's going to happen in the post market environment.

And we are starting to get some data about what's happening with snus, for example. We're in a post market situation with that now.

And there are no modified risk claims being made in the advertising and in
fact, there is very little uptake of this product on a regular basis.

And if you have a look at, at least in some of the work that I'm doing where the product has been available to people in these former test markets for about five years now, smokers perceive them as being less enjoyable than their cigarettes.

I mean they really prefer their cigarettes on lots of dimensions. So I think we need to keep in mind that the real disaster out there is the fact that the smoking prevalence in the population has been stagnant for the past five years, and given the current level of advertising not much looks like it's going to happen to change that.

So I don't know, just something to keep in mind.

MR. HOLTZ: Yes, Dr. Ling?

DR. LING: I just wanted to add in thinking, because Lois mentioned the work she's doing looking at post market, we are
doing a little bit of work looking at the snus
use among young adults, a high risk population
of young adults in bars and nightclubs.

And in that population which
would, you would think, not be a typical harm
reduction target, our surveys are seeing much
higher rates of past month use than Lois is
seeing in her population based sample.

So I think you can get data and
fairly quickly in sort of a post market
situation of populations potentially taking up
the product that should not be if you're
thinking from a public health standpoint.

A challenge I think for us is
that, you know, Dr. Tomar also mentioned that
we are already seeing for several years now in
existing surveillance, increases in smokeless
tobacco use among youth.

Again a population that would not
be an ideal, you know, harm reduction target
and there is no current plan as to how to
respond to those observations. So what we
really need in thinking about post market surveillance, which I'll just say now because I may not be here for the next panel, is to plan ahead and have a pre-market agreement about what is going to happen immediately if we are seeing these patterns of use or uptake amongst the wrong populations rather than, you know, getting in a situation where we're seeing something happening and now we have to go to court or, you know, we have to start a long process to try to create a response to that.

MR. HOLTZ: You know, one thing I think our experience with understanding tobacco marketing for the public health community, there were quite a few revelations in the documents that came out a number of years ago that had been internal documents, indicating that the industry knew a lot of things about the consumers that a lot of public health people maybe, you know, it was beyond what public health people generally
knew.

So in this pre-market testing should there be something in the standards or in the protocols about disclosure, about what the industry does and what you tell?

You know, to use the analogy of pharmaceutical marketing, the major medical journals will no longer accept a report on a trial that wasn't registered in advance, so that to try to keep industry from hiding the results of trials that didn't turn out the way they wanted.

Should there be things like that in these requirements saying you have to disclose all of your documents?

And obviously a company on the other hand is going to say well, if we give it up then our competitors are just going to get a free ride.

So how do you deal with tapping that industry knowledge about likely consumer behavior?
DR. BIENER: I think that disclosure at a very high level is very important. And I understand the problems with trade secrets or those sorts of issues.

But it seems to me that here, I'll lay it on the FDA also, that there is internal work that can be done within the agency to analyze that information without making it public. And I think it's vitally important.

MS. GRAVES: I think the statutes require that with an application we disclose all study results and both qualitative and quantitative information.

So we would definitely be complying with that and understand why it's there.

DR. LING: I would add to that. That I think that the, you know, the research is very sophisticated and has been for many years, and so that I agree the tobacco companies have known a lot of things that could be disclosed, and not just maybe the
results of the research.

But should the FDA find it informative, I think that the raw data or the original, you know, recordings of qualitative and, you know, the survey design, all of that should be made available.

DR. HASTAK: I was just going to say, I think it's imperative I think that you get that kind of data, I mean I don't know how you get it and what the political issues are.

But, you know, I'll talk about my experience at the FTC where certainly in litigation, but also when the FTC holds workshops on issues like environmental claims, for example, and how to regulate them, we're developing guides for industry.

That whenever they put a request for comments out there they request research, and often the FTC gets a lot of consumer research from the industry.

Now the situation is a little bit different, but what I find when I look at that
kind of research is that it's often conflicting.

And, you know, somebody made this point that, you know, social science type of studies or copytests and so on, are not the kind of hard science that you might see in other settings when you are regulating tobacco.

And, you know, very subtle issues like what you're presenting to consumers, is it out of context? Is it within context? You know, what are the questions that you ask, are they leading? Are you creating demand artifacts?

So I think looking at a lot of studies, certainly in my experience, has been very helpful in trying to get a -- that plus the fact that, you know, the FTC certainly has limited resources.

I'm sure that's true at the FDA, so relying on a single study I think is very hazardous in these situations. And so getting
the data from the industry, however you get it, would be quite important.

DR. SHIFFMAN: I think again that the analogy to the other part of the, to CDER where they're also dealing with, you know, regulating industry in terms of drug development is apt.

And if you submit an application say for approval of a new drug, you're expected to submit the protocols, ideally in advance, and you submit the raw data in a way that the FDA can do their own damn analysis, and see if they come to the same conclusion from the same data.

And furthermore, the FDA in that instance, and I suspect in this instance, has the authority to audit not only the data that you send, but to go to the sites, make sure that the research was actually done in the way that was specified and so on.

I want to raise what I think is a thorny issue that is at a tangent to this,
which is again let's look at drug development.
A lot of these studies get done in
collaboration with independent or academic
researchers.

And while that has not been
completely unproblematic, it's another way in
which there's some transparency because it's
not just the sponsor who's doing the research.

And I think this meeting, for
example, is a beginning of a dialogue and
collaboration, but I think there are some at
the moment at least, some significant barriers
to that sort of collaboration that I think
we're going to have to work through.

Because in some ways, we in the
public health community have been saying for
not years but decades, you know, tobacco
companies should be doing research on these
toxicological factors, on these behavioral
factors.

Now under FDA pressure if you will
the companies are going to be doing that, I
think that makes our position that oh, but we can't possibly work with you untenable.

I think that we're going to have to consider, how does this research take place? What's the role of academic and independent researchers working with the companies to do research for submission to FDA?

MR. HOLTZ: You know, we just had the comment about that the FDA should require youth to be included, since clearly if there was no new initiation among youth though we would see a dramatic change over time in tobacco use prevalence.

But then the industry position, public position is now that no, they don't test in underage populations or even, you know, in people who aren't currently using the product.

So should the FDA require that the industry go ahead and study in nonsmokers, in potentially vulnerable youth populations, or
should that be done by somebody else?

And how does that feed then into
the understanding on, again focusing on the
pre-market environment of what the likely
impact of a new product's going to be in the
actual world?

DR. LING: I would agree. Maybe
it's because of my background, but I get very
nervous when thinking about having the tobacco
companies do market research on youth, even
though they have done it in the past and have
continued to do it under the guise of, you
know, nominal youth smoking prevention
programs.

It provided great cover for
tobacco companies to do surveys on young
people and figure out, you know, what their
motivations to smoke were.

So I would prefer that, I think
that youth need to be tested because, you
know, if you look at the advertising you need
to know whether it appeals to youth and
whether they're interested in the product, et cetera.

I would prefer that that be done by an independent party so that, and that the results of that research be kept separate from, you know, the marketing activities --

MR. HOLTZ: But you would see it as something that would be required of applicants that they then in some fashion commission an independent party to answer certain questions.

DR. LING: Yes, and I think there has been, you know, and certainly within the academic world there have been independent parties, you know, conducting research on youth appeal of tobacco products.

The research on the appeal of flavored cigarettes amongst youth was conducted by independent researchers.

MR. HOLTZ: Ms. Graves, what do you think is --

MS. GRAVES: We are just seeking
clarity. If we have an application for a product, a modified risk tobacco product, obviously it is our case to make in terms of what we believe based on our research, the net benefit to the population is as well as trying to measure and evaluate any unintended consequences.

So at the same time that Dr. Ling is concerned about us doing research among youth, we would have concerns about somebody else doing research on an application. It's similar to if a pharmaceutical company having a new drug application and somebody else doing research and presenting it in with their application or alongside.

And so we are just seeking clarity. We have a policy that we do not research among anyone other than current adult tobacco users.

We have explored adult non-tobacco users as we've looked at these provisions, the
population heath standard, and trying to
anticipate what might be required there.

We would just need the cover in
terms of doing it that it was required and
expected along with our applications through
clear guidance and regulation from the FDA.

MR. HOLTZ: Dr. Hastak, what would
you think if there was something where they'd
say we've got to study youth.

The industry, we're not sure about
letting the industry do it, and they say we're
coming to you with a contract for studying the
youth perceptions of this potential product.

And by the way there are a lot of
trade secrets involved so no, you can't go
publish this. What do you do?

DR. HASTAK: Well, personally for
me it would be a hard sell. But I mean, I'm
sort of thinking about the issue a little bit.
I haven't thought about this particular issue.

I think it comes up in litigation
and other situations where there is all these
that concern that, you know, both parties or
one of the parties might be producing
empirical research, but the sponsor of the
research has an interest in the outcome of the
case.

And so there has been this talk
about, for example, having courts in that
situation identify an independent third party
researcher, potentially an academic or
somebody else whose research would be funded
by, you know, the plaintiffs as well as the
defendants. I haven't seen it go very far.

More often than not what you have
is kind of this system, at least the ones that
I see, in the litigation I see where both
parties tend to produce research.

Both parties tend to produce
experts, and it's kind of this interchange
between the experts and the presentation of
data that often points to different
conclusions that needs to be resolved.

And at least my sense is that
model may be a worthwhile model to think about here. I mean, you know, companies could do research, but it seems to me if a research is sponsored by a company, as kind of just an independent consumer I would be suspicious of that.

But I can see companies being suspicious of, you know, in litigation I see companies very suspicious of research that I do for the FTC.

Their attitude is gee, you know, you want the FTC to win, right? I mean, so and I'd keep pointing that that's not the way I operate, but that's not how they -- you know, and some of this is simply kind of engaging the other side to try and influence the outcome.

But it seems to me a process whereby companies could do research that certainly carefully vetted, but is funded by them.

But there is other research, and I
don't how you'd get to that other research
that is created that's more independent or
even it's being done by people who have a
somewhat different point of view as we have
here.

I mean, I'm listening to
researchers here and a lot of researchers,
very independent researchers, clearly seem to
have points of view based on their research.
That's not typical in the work that I do.

So I think that engagement may
potentially be worth exploring.

MS. GRAVES: Another option would
be with FDA guidance potentially similar to
guidance on over-the-counter products and
comprehension studies that might lay out a
framework, some study design elements,
disclosures, you know, whatever things might
be of concern researching among youth that
would be a defined protocol that we would
follow to mitigate some of the concerns.

Or conversely, submit our
methodology studies on protocol to the FDA prior to doing any research with that audience, for approval.

DR. SHIFFMAN: I would agree with that. I think that regulation and openness changes everything. So there are two reasons that people are suspicious of letting the industry do the research.

One is that for a long time research was being done in order to sell cigarettes to minors, and that was being denied, and because there's a history of the research being not only kept secret but used to the industry's own ends.

But I think if we're talking about research which is mandated by FDA, which is submitted to FDA and which might be done as Ms. Graves is saying, under pre-specified protocols, you know, there could be room for variation.

But again on the drug side, the FDA gives sponsors a sense of this is the kind
of research -- you know, you don't make it up anew each time, you're just supposed to run a placebo-controlled study.

It has to be adequately powered.

It's frankly in the sponsor's interest to have the FDA review the protocol in advance, because the worst thing is you do the research, you submit it and FDA says, what the hell were you thinking? This isn't the right study.

So I do think that their regulatory context creates a new world and that some mixture of FDA saying, and this might take time to develop, this is the kind of study, this is the protocol that we want to see.

And FDA reviewing sponsor proposed protocols that again open at least to FDA and ideally to everyone else, I think would be a way to proceed.

MR. HOLTZ: As we've mentioned in several of these panels, there is the
background of the products, tobacco products that are out there now and potentially new products that come along that don't make any health claims, that don't apply for approval under the modified risk tobacco products scenario.

How does that affect what you would ask of these new products? Because if, certainly it seems that under the current environment if a company can go out and do whatever testing it wants as much or as little as secret as it wants as long as it doesn't make a health claim there's, the FDA would not have a role in determining what pre-market testing to do.

Does that background, how does that influence what you would want to see required of these modified risk tobacco products in order to get closer to the goal of reducing risk and harms for individuals and populations?

DR. BIENER: My impression is that
the products that are now out there without making modified risk claims are the ones that we're talking about.

That what's going to happen is that the advertising of these products would change. So I mean I suppose --

MR. HOLTZ: It would probably be under a different section of the regulations than a, that's not under the modified risk tobacco product section.

MS. GRAVES: Well, they could be submitted as an MRP application and then claims would be added. And let me just, did I interrupt you or were you finished?

MR. HOLTZ: No.

DR. BIENER: No.

MS. GRAVES: Okay, let me just, we have always placed our marketing efforts on switching adult tobacco users to our products, competitive adult tobacco users to our products.

It is extremely hard to switch a
Marlboro smoker or a Newport smoker to a Camel. And that's basically the same product. I mean, when you're talking about combustible products that have existed in the market today, they're basically commodities.

There's not a wide range of difference between those products. It's the brand. Tobacco users are very loyal to their usual brand, their usual product.

So even with like to like products it's very, very difficult to switch them. So then you talk about, you know, for us we believe that smokeless tobacco products such as Snus and dissolvables have a tremendous opportunity to reduce population harm.

And we are putting those products in the market today without the benefit of being able to state what we know and don't know about those products in terms of risk and harm.

We have to have a reason to get people to try it that are currently using
tobacco products, to try it. They have to have a compelling reason why.

Tobacco products are consumer packaged goods. They're not pharmaceutical products, they're not over-the-counter medicines.

They are consumer packaged goods. People are very loyal. They like what they like. They don't switch brands, much less product categories easily.

The communication that we have today on Snus and would probably continue that thought as we market the dissolvable products, is all about giving consumers that are using other products, primarily adult smokers, a reason why to try Snus, for example, cannot talk about the health benefits.

And to your point, as much as we are trying to give them a compelling reason which is just quite simply functional in terms of convenience.

You have to look at what they're
using and look at how you can establish a point of difference for your product and give them a reason just to try it.

Because this disposition funnel with any adoption is a long process. They have to be aware of it.

They have to understand and have, understand the communication of what the point of difference is and become interested in it then try it, use it, consider it, you know, more and more along with their usual brand. And then, you know, ultimately adopt it and switch.

That is a very long process. What we've learned from our test markets with Snus is it can take, you know, 12 months to 18 months and so yes, you're going to see some dual use in that process.

But just because the message might be trial or it might be when you can't smoke, it doesn't mean that that is our objective. Because clearly, our objective would never be
to the entire adult smoking population just try it.

Just because what we say to consumers and the way we try to present motivation for them to take action and the action that we would want them to take, just give it a try, or use it, you know, when it's inconvenient to use your regular product.

It doesn't mean that's our objective. At the end of the day we want to switch adult smokers that will not quit, if you can figure out who they are, over to one of our smokeless products.

Or at least if they're going to continue to smoke a combustible that they would smoke one of our combustible products until they would hopefully quit or switch to smokeless.

And the process in getting that switch behavior is to create a compelling reason, and with Snus it is quite simply not that we want to promote dual use. We don't.
We want to switch, we want Camel Snus to become the UB for every adult smoker out there because we believe there's a health benefit.

And the way in which to go about that without being able to talk about harm reduction or health benefits is to offer a consumer benefit in terms of convenience and ask them to try it and start to use it with the ultimate objective to switch.

MR. HOLTZ: Dr. Ling?

DR. LING: I'm glad this is not a panel to build consensus because I'm going to have a hard time coming to consensus on that.

There's a tremendous number of examples of tobacco marketing being used not just to switch, to convince current users to switch brands.

That may be one objective of marketing, but certainly there's a very well documented history of using tobacco marketing to recruit new users.
And I think with regards to the Snus products, if you look at the profiles of who is adopting the Snus products as best as we can tell now, it does look like it's quite, more popular amongst younger audiences.

And the practices like having, you know, the Ingas dressed up like they're from Sweden and going out to the bars and clubs and giving a free sample, you know, to young adults in a, you know, in a bar environment where they're maybe drinking alcohol and not making an informed choice, is really not the type of marketing activity you would expect to see to convince smokers who cannot quit, you know, to try a safer product.

And we do know that youth do initiate more with lighter products now, and I do think the health message may also encourage, you know, young people to, you know, take up the product because it's not so dangerous.
initiation and just the history, it is not consistent with a purely switching objective.

MR. HOLTZ: I want to get to the summary statements but, Dr. Ling, one point I did want to get to before we wrap up here, is the communication that goes on that at least appears to be out of the control of industry, how does that factor in into the pre-market environment primarily?

What kinds of information would you think the FDA should look at in terms of what happens in social marketing, what people are telling each other, should that be, should applicants be required to monitor what's happening beyond what they are specifically putting out?

DR. LING: I'm glad you brought that up because I do think that those kind of retweeting, constant retweeting of information and the transmission and getting smokers to talk about the product to their friends, you know, is actually part of the marketing plans
of, you know, of previous PRABs, and can be of
current products. I would agree this an
area that definitely needs some kind of
monitoring and, you know, it's difficult to
tell exactly, you know, how that can be done.

But it's certainly an area that
seems to be more and more important in terms
of getting messages about the product out
there.

And, you know, the tobacco
companies benefit from maybe not being
directly responsible for what a consumer says
about the product, but if you look at, you
know, the websites or the blogs about, you
know, Snus products or the electronic
cigarette products, you know, most of the
health claims are put in the form of
testimonials which the company may not be
officially responsible for but do carry a very
strong message that affects consumer
perception.

MR. HOLTZ: All right. Well, then
let's go down and if there are anything that
we should have brought up that we didn't, or
just to summarize your thoughts this morning.

                   Dr. Biener?

               DR. BIENER: Well, I think in an
ideal world there would be -- well, in an
ideal world nobody would use tobacco at all.
But in a somewhat less than ideal world,
person would recognize that there is a
continuum of risk and that moving to a less
harmful product is going to be better for
them.

             And I would hope that we would
think about ways to convey messages to the
population that can move people to reduce risk
and also then create products that are less
risky at the same time.

             And openness between the industry
and the scientists and the regulators I think
is a really important thing to do whatever we
can to promote, and I'm happy that at least
we've started to do that here.
MR. HOLTZ: Okay, Ms. Graves?

MS. GRAVES: I echo that as well.

Thank you, FDA, for allowing this workshop and allowing us to participate.

As Dr. Biener said, some people are never going to quit using tobacco products and it's idealistic to assume that tobacco usage would ever go to zero.

Therefore, I believe the tobacco companies and public health community would agree that there's a huge opportunity here to create products that, in fact, would reduce population harm or have great potential to do that and to allow them into the market to evaluate the real outcome in the case of a reduced exposure product.

With this opportunity does come an obligation to minimize to the extent that you can unintended consequences by clarity of message in your communication, in terms of reduced exposure making sure that you have, you don't have consumer take-aways, that
they're not perceiving things differently than
what you're communicating.

In the case of reduced risk
products that they clearly understand that
there are still risks, that reduced risk
doesn't mean no risk.

And then finally, Section 911 does
provide for uncertainty. So target levels for
consumer takeaway, related messaging and
comprehension should not be overly burdensome
to suggest that the product could not go into
the market where you can get actual consumer
behavior information to validate what you
assume or projected in the pre-market
analysis.

MR. HOLTZ: Okay. Dr. Hastak?

DR. HASTAK: Just a couple of
issues I'd like to mention. I think a number
of people have talked about this, you know,
some form of consumer research to assess
whether advertising for these kinds of
products is truthful but misleading.
I think it's important. You know, but based certainly on my experience I would say, I hate to make predictions without data, but I would say it's very likely that if you give consumers a message that says this product has less of some harmful substance, they are going to make the inference that the product is safer for them.

And I just think it's highly unlikely that without any qualifiers that people won't take that message. So I think the more interesting issue from my perspective is the issue of disclosures.

Can you put some information in the advertising, on the packaging that can correct that misperception, not boomerang, not go overboard, but effectively sort of educate or influence consumer comprehension?

And I was actually very impressed with the study that Dr. Biener mentioned about consumer education. I think those results are wonderful.
Unfortunately, in my experience in trying to devise these disclosures I've not been as successful. What I've found is that it's very difficult to craft a disclosure that essentially is going against, you know, consumer knowledge, consumer expectations.

If you have less sodium in a product, it's going to be healthier. If you have less fat, it's going to be healthier. If you have less of some toxic substance, it's going to be safer.

So I think the FDA needs to look at kind of both research that helps devise these, create these disclosures perhaps some good qualitative research, and then kind of extensive testing so we have something that comes close even if it isn't perfect, to communicate effectively with consumers. Thank you.

MR. HOLTZ: Dr. Ling?

DR. LING: Yes, I just wanted to express my appreciation again for being able
to participate.

I think in terms of brands, I think that the point that was made about how the brand versus the message can be at odds with each other and how that's difficult for consumers to interpret is quite interesting.

That does really lead me to encourage the FDA to think skeptically about whether or not it makes sense to have reduced risk products and conventional products with the same brand, as consumers may just lump the risk to the entire brand family.

And secondary, in terms of thinking about disclosures I would encourage the FDA to think again perhaps about the corrective statements that were put forward by Judge Kessler with the RICO case which I haven't seen much happen with them lately, but they were pretty strong corrective statements that might be of use in correcting consumer misperceptions.

MR. HOLTZ: Dr. Shiffman?
DR. SHIFFMAN: I have to say that I share perhaps Dr. Hastak's pessimism about crafting a balanced message, and don't share Lois's optimism, but it may be that she's just more capable at communication than the rest of us.

But this is a very complex message if you think about the debates here among experts with decades of experience, and how hard it's been to sort through exposure versus harm versus biological effect.

The idea that Joe Camel is going to, or Joe Citizen is going to understand that I think is a stretch.

And that's why I think it is important that we have extensive pre-market testing not only of the ads but again the broader messaging. And I think it can extend to behavior.

I think again this industry and others regularly do behavioral tests by doing test markets, and that that's a fitting
setting in which to get one step closer to reality before putting things into the market.

And I think that the standards should certainly be no lower than those in practice for advertising under the Lanham Act, which is to say that you really have to achieve appropriate understanding in a very high proportion of exposed consumers.

And I think in all of this research I think FDA has a very strong role I think in helping to answer these questions. That is, to define what kind of research needs to be done down to defining protocols for carrying out some of this research which also will lead to uniformity.

You don't want to be making a decision for one product based on one kind of a research and for a different product based on a completely different research model. So I think it's important for FDA to be proactive there.
And I'll just join with the rest of the panelists in thanking FDA for creating this opportunity for dialogue both among academic colleagues but also between FDA and the tobacco industry and researchers.

And I hope it's not the end but really the beginning of a more extensive dialogue and collaboration with FDA industry and researchers.

MR. HOLTZ: Thank you very much there, Panel. And let's try to stay a little bit ahead of schedule. The agenda says we're reconvening at 1:30, but let's make it 1:15.

(Whereupon, the above-entitled matter went off the record at 12:05 p.m. and resumed at 1:17 p.m.)

MR. HOLTZ: All right. Welcome back to the last session of the Scientific Evaluation of Modified Risk Tobacco Product Applications. And this public workshop again, is meant to just get comments and views of

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various experts in the field into the record. Not a consensus or any kind of recommendation, but to try to cover as much of the waterfront as we can on this topic.

And to reintroduce myself, I'm Andrew Holtz. I'm an independent journalist and so the comments I say are just my own questions trying to move the conversation along and don't have any official standing.

You should have some sort of forms in your folders where it will give you an opportunity for feedback on this session. Please do fill them out. There are some experimental facets of this kind of meeting, and so anything that you can tell the FDA about what you got out of it will be helpful for the future.

And then again, please do make sure that you have turned down your cell phones and other devices, make sure I did it. Yes, that would be embarrassing.

In this final session we will look
at the postmarket surveillance and studies of
commercially marketed modified risk tobacco
products. And again, I will be introducing
each of the panelists in turn, and then they
will get a few minutes to just toss out some
comments before we start the general
discussion.

Our first speaker will be Dr.
David Abrams, who is Professor of Health,
Behavior, and Society at the Johns Hopkins
Bloomberg School of Public Health, and
Executive Director of the Schroeder Institute
for Tobacco Research and Policy Studies at
Legacy.

As former Director of the Office
of Behavioral and Social Sciences Research at
NIH, Dr. Abrams is a Clinical Health
Psychologist. He holds a B.S.C. in Computer
Science and Psychology from the University of
Witwatersrand, Johannesburg, South Africa, and
a Doctorate in Clinical Psychology from
Rutgers University.
Dr. Abrams is lead author of the Tobacco Dependence Treatment Handbook, a Guide to Best Practices, a recipient of a Book of the Year Award.

He was a member of the Board of Scientific Advisors at the National Cancer Institute, served on the Robert Wood Johnson Foundation's Transdisciplinary Tobacco Etiology Research Network, and several Institute of Medicine expert committees, including ending the tobacco problem blueprint for the nation.

Dr. Abrams provides scientific leadership in tobacco control by embracing transdisciplinary and translational research strategies. He has extensive experience in testing theory, in research design, and in the measurement of mechanisms of behavior change and outcomes.

Since 2009 he has focused on the role research can play in informing the regulatory decisions of the FDA Center for
Tobacco Products.

This includes coordinating development of a strategic research agenda to inform FDA, convening expert thought leaders, and conducting rapid research and providing knowledge synthesis in areas of FDA priority, such as examining mentholated cigarettes in public health, reduced harm products, e-cigarettes and public perceptions of potential FDA regulations. Dr. Abrams?

DR. ABRAMS: Thank you. And I'd like to thank the FDA for holding this precedent setting conference. It's an enormous opportunity to look at the potential leverage we have to improve the public's health and save lives, and reduce the harms of tobacco products.

Would just like to make several points, in no particular priority order. First, I think with respect to postmarket surveillance, and I think this applies really to the whole continuum of things we've been
talking about up to now.

To me it's very important that we have some kind of conceptual framework, blueprint, or roadmap to drive and organize the priorities, parameters, and guidelines. Because clearly, one size does not fit all, and we can't apply the same rules to any individual product that may come on the market.

So I think it's very important that we begin to develop the kind of framework that Dr. Shields for example, presented in the first day, but much more specific to this particular topic.

And in particular to how I think we should look at the obvious and natural tensions where there's no clear answer. And one of the tensions that I noticed in this discussion is that there's somewhat of an artificial distinction between premarket testing, rollout of a product, and postmarket surveillance.
And in an era where we've got rapid ability to do tracking and real-time analysis of viral spread, and implementation, and adoption of new products, I think we have to look at the fact that there might be an opportunity to not push the idea that almost everything that is long-term and definitive has to come in postmarket surveillance.

So I think it's very important that postmarket surveillance doesn't become just the catch-all bin for, you know, all the definitive stuff has to be done later, and long-term, and in postmarket surveillance.

I do think almost everything that ultimately you'd want to validate in postmarket surveillance could begin with a high-bar and criteria in premarket testing, and in the early rollout and implementation, where you could do tracking and have an early warning sort of red-flag system in place, particularly with new technologies.

So the second point I want to make
is that I think it would be also useful, prior
to postmarket surveillance, to think about
what we do in data safety monitoring boards.

    And that might be that when we do
premarket requirements, that we have some red
flag messages and stop action, that if you
find the following things, this will be
removed from the marketplace, and do that a
priori, as opposed to waiting for some kind of
debate with vague outcomes and vague stop
criteria that all would be again, put on the
burden of postmarket surveillance.

    So a third point is that I think
it's really important and we haven't done
enough of this, to take lessons from marketing
and entrepreneurial industries that are using
new technology in new ways.

    So for example, I think there's a
unique opportunity to combine multi-level and
multi modal assessments in ways that we
probably haven't done as aggressively or as
well as we should, from an either academic or
regulatory perspective.

And I'll give you just one example of that, assuming that we are going to fund this national longitudinal study where we have a very large cohort that will be followed longitudinally over time.

There's an enormous opportunity to use that representative sample to then select purposive and small subgroups, in order to do rapid surveillance and testing of key emergent issues and questions.

So for example, if you are sampling from that known group, you have much stronger ability to generalize and show how whatever you're sampling could be scaled up to evaluate population impact and public health benefit.

So one example might be that you see an emerging product like dual use of say, e-cigarettes, Snus, and cigarettes. You could preselect a group from that NLST at random, and invite them to engage in an ecologic
momentary assessment, say one month intensive
follow-up with web-based and smartphone-based
real-time recording of their actual use and
exposure of all three products.

And that in turn could become much
more solid parameters to inform very specific
simulation models, or even take those
behaviors and then begin to do human
laboratory studies modeled after those
parameters.

All the way to perhaps, being able
to fully quantify and then scale-up simulation
models that would much more accurately reflect
and be able to operationalize public health
impact.

So, you know, my last comment
based on that is that I think an integration
of things like agent-based modeling, fully
informed by actual data that is now collected
in real-time from population representative
samples, would improve the kinds of simulation
modeling that we have done up to now which is
often criticized, because the parameters and assumptions are quite variable and often not driven by data.

So the idea of doing very explicit simulation modeling is not just to do modeling for modeling sake, but to help us make operational and transparent, be explicit parameters that feed from individual differences and variation in patents of use behavior, not knowledge and attitudes but actual behavior.

And begin to then scale that up into clusters and models that would truly tell us how to get from individual harm benefit to population level impact, including feedback loops of unintended consequences like dual use leading to longer duration, even though it has reduced, let's say use of combustible cigarettes within that longer duration.

MR. HOLTZ: Dr. Abrams, it's been, wrap up.

DR. ABRAMS: So in conclusion, you
know, I just think there's a lot of exciting opportunities here if we think about postmarket surveillance in creative ways, and see it as part of a continuum from premarket testing to rollout to this sort of ultimate stops in the process.

To allow only harm benefits to the population to go forward and to make sure that unintended consequences do not occur, or if they occur they are caught extremely early and rapidly and that aggressive action can be taken.

MR. HOLTZ: Thank you. Our next speaker is Dr. Michael Borgerding. He is a Senior Director in the Research and Development Department of R.J. Reynolds Tobacco Company, and he's made some significant contributions to the understanding of tobacco and tobacco smoke chemistry since joining the company in 1980.

He is widely recognized for his expertise in the area of analytical method
development and validation for his leadership
and efforts to characterize smoke arising from
new technology cigarettes intended to reduce
the risks associated with smoking.

And for collaborative efforts with
state and federal regulators in the United
States and Canada that require the testing of
mainstream cigarette smoke.

Dr. Borgerding currently leads a
team of scientists that are responsible for
conducting clinical studies to evaluate new
and existing tobacco products.

Such studies include measurements
of tobacco product use behaviors, quality of
life changes, biomarkers of exposure, and
biomarkers of potential harm.

The clinical studies team is also
responsible for the development and validation
of new biomarkers and the development of
clinical study designs to support postmarket
surveillance of tobacco products. Dr. Borgerding?
DR. BORGERDING: Thank you. I also would like to thank the Center for Tobacco Products for convening this very important meeting and for inviting me to participate.

Much like Dr. Abrams, I think my primary message is around integration. Postmarket studies and postmarket surveillance have the potential to address a number of program goals.

Those are goals such as how the marketplace may be changing with the introduction of an MRTP. Studies that might confirm expected results, that is reductions in exposure to toxicants, and then ways to monitor for unintended consequences.

But I do draw distinction between studies and surveillance, and I'll show you that in the next couple of moments.

So where do clinical endpoints potentially fit in? My remarks will be limited to clinical endpoints, but I would
suggest to you that they fit in in three ways.

First of all in the preapproval process, the request for MRTP label, labeling, and advertising approval. They fit into the postmarketing study of an MRTP, after it's been approved and is in the marketplace.

And as importantly, clinical endpoints fit into the perspective surveillance of tobacco products to establish nationally representative ranges for tobacco product categories and control groups.

I think it's critically important that we consider harmonizing the testing that would be done in all three of these areas, so that we would have test protocols and endpoints that were validated and consistent amongst these three different areas.

So I'd like to speak briefly to each of those. First of all in terms of the request for approval, clinical study results may be one element of an approval application.

And such a study could be
conducted with one of two types of individuals. Either for example, smokers that are being switched to an MRTP.

Or if the MRTP has been in the marketplace for a sufficient period of time, there may be able to be the ability to study natural adopters.

More often than not, I would expect it's probably going to be a switching study, rather than an adopter study for this approval process.

These types of endpoints, clinical endpoints, biomarkers of exposure endpoints, I would suggest are direct evidence for an application around reduced exposure.

I would also suggest to you that in terms of reduced exposure, while we have the ability according to the act to communicate the reduced presence of a substance, or the reduced exposure to a substance, these are either implied or expressed claims around the same topic, and
should be based upon the same type of scientific information and data.

In terms of postmarket, clinical studies have the ability to provide information for individuals that actually have adopted the modified risk tobacco product and used it for a substantial period of time. And so they're appropriate for understanding exposure.

They're most appropriate for MRTPs which are being communicated in terms of a reduced exposure message, and when there's not the ability to have product relevant epidemiology data for the product in question.

There are some practical limitations, and these are just really around timing. If we considered postmarket surveillance from a 5-year time horizon, there needs for a new MRTP to be introduced.

There needs to be time for smokers for example to become aware of it, for them to adopt it as their usual brand, and then for a
clinical study to be conducted.

Given the timing for each of those elements, it's probably only realistic to expect one clinical study within a first 5-year time frame. And so that's just a practical consideration.

The third area that I'd like to touch on before concluding, is the concept of perspective surveillance of tobacco products. And in terms of this I would suggest that it would be something that would be ongoing, at some specified frequency.

And that it would be a government sponsored program focused on established tobacco product categories. It would also include control groups, non-tobacco users, former smokers, various groups such as that. It would include groups of dual and poly tobacco product use categories as well.

In terms of such a program, what types of testing or studies should be conducted, clearly collecting information such
as demographic information, tobacco product use information, tobacco product use history, which different types of tobacco products might have been used in the past, perception testing, biomarkers of exposure, biomarkers of effect, quality of life measures, and health outcomes.

It's most important that all of these methodologies would be fit for purpose and that they would be validated. And I think we all recognize that that will take some time.

Of course, why do such a program? It may seem a bit ambitious. It provides a basis for monitoring the transformation and the evolution of the U.S. marketplace as MRTPs become part of that marketplace.

It also provides a basis for comparison of results from a specific MRTP postmarket surveillance study, to nationally established norms or ranges. And then finally, provides a basis for conducting
testing via uniform validated protocols.

And so again, much like Dr. Abrams, I would suggest that integration is critically important and postmarket surveillance does not stand alone, we have to consider it in the broader context.

MR. HOLTZ: Okay, thank you. Our third panelist is Christine Delnevo, is that?

DR. DELNEVO: That's correct.

MR. HOLTZ: Good enough. A Ph.D. and a M.P.H. She's an Associate Professor and Interim Chair of the Department of Health Education and Behavioral Science at the UMDNJ School of Public Health, and the Founding Director of the Center for Tobacco Surveillance and Evaluation Research.

Her research expertise focuses on tobacco use behavior trends, particularly non-cigarette tobacco products, including modified risk tobacco products, as well as methodological research to improve tobacco use surveillance.
Dr. Delnevo is currently the Principal Investigator of an NIH NCI Research Grant to examine smokeless tobacco use in the general U.S. population. She provides survey content expertise on non-cigarette tobacco use to NCI on a regular basis. She is published extensively on the patterns of tobacco use behavior and dependence, and is a contributing author to two upcoming Surgeon General reports on tobacco use.

DR. DELNEVO: Thank you. And thank you to the FDA for providing us this forum to have this important discussion.

So I actually want to start my comments, and my comments I'm drawing from, the broader tobacco controls surveillance experience. Because we've been doing ongoing surveillance for numerous years and there is much for us I think, to learn from there with regards to starting points, with regards to postmarket surveillance for modified risk
tobacco products.

So the two areas that I wanted to highlight initially are challenges with regards to both sampling and instrumentations. So with regards to sampling, something to consider at least initially, that there is going to low rates of awareness, and trial, and adoption with these products.

And so, some preliminary data we have from our 18 to 34-year-old national survey shows that young adults, less than 15 percent have heard of dissolvables, and that five percent report some sort of trial with it.

It's not surprising when you look at market scanner data from Nielsen that shows the dissolvables currently make up less than one percent of the total smokeless market.

I actually looked earlier today at the 2009 NSDUH to look at Camel Snus, and of the 55,000 participants in the 2009 NSDUH, there were 84 Camel snus users.
So the point here with regards to sampling at least initially is, when we're talking about population level nationally representative data, we're going to be looking for the needle in the haystack to try to find these individuals.

And that I think is something that we need to take consideration when we start the development of these systems.

With regards to instrumentation, we have a history at least, with having some pretty good measures as it reflects to cigarette use. But we really have a long way to go with regards to other tobacco products.

There's no standardization there, and cognitive testing suggests that tobacco users don't really do a very good job at distinguishing across the product categories.

Is it chew? Is it snuff? Is it dip? Their understandings of the terms, I mean, it even goes so far as when we look at little cigar users. When you look at
cigarette brands, you have people who are identifying as cigarette smokers, reporting actually a little cigar brand.

So for the consumers there is this issue of whether or not the terminologies and our questions are ready to properly address the postmarket surveillance.

And in addition, we've got challenges in survey research in general right now with response rates, differences by mode, issues regarding question construction and context effects.

And so all of these things are going to have to be factored in. And I think the take-away is that, whatever this postmarket surveillance system is going to be for these products, it's going to be complex.

And there's going to need to be this balance between innovation and innovative approaches, and balancing the need for nationally representative information.

And so to remind folks, one of the
key purposes of surveillance is to detect trends signaling changes in behaviors. And so I think we need to consider early detection systems to inform the more complex surveillance that we're going to need to look at.

And so there's been other examples outside of tobacco. You know, Google has their flu tracker, which has been shown to be able to pick up, I think about two weeks before the CDC actually can report the actual cases, with pretty good accuracy what's going on with the flu.

There's some anecdotal data that, you know, sales on over-the-counter pharmaceutical products has been useful to detect outbreaks of gastrointestinal illnesses. And I actually think that market scanner data could potentially provide this for us when we're looking at modified risk tobacco products.

I'm not going to go over this.
slide in a lot of detail, but Nielsen is
certainly a source of market scanner data.
We've maintained this data for the past five
years, for both smokeless tobacco and cigars.

    And the product features, we can
really drill down to very specific things like
the types of products, the packaging, the use
of the flavorings, and look at those data over
time to see what's driving the use.

    And so very quickly, this is
what's been going on with dissolvables over
the last five to six years. Dissolvables are
not new on the market, but as you can see when
R.J.R. pulled Camel dissolvables in 2010, the
units actually went down.

    But one of the things I don't hear
very many people talking about, is 50 percent
of the market share in '09 and 2010 was
actually stonewalled. You know, a lot of the
attention right now is focused on Camel
dissolvables and there are other products out
there.
With regards to snus, we did have a pretty big increase in volume from '09 to 2010, and you can see the comparative growth for Camel and the Marlboro products.

One of the things that I think is interesting is these products are flavored. And the Camel products are more flavored than the Marlboro products, and they're being used with regards to mint and wintergreen flavorings, at least the predominant flavors that are being utilized.

One of the things we've looked at with the Nielsen data is regional variations. And one of the findings that we came across was that, in areas in the U.S. with high per capita smokeless tobacco use, the market share for Camel snus is low.

But in areas where there is low per capita smokeless tobacco use, Camel snus has actually notable market share and they're doing, relative to the other smokeless products, they're doing very well.
And so we think that finding is consistent with the premise that it's designed for the cigarette smoker and not for the smokeless user. And the only caveat I would make is that market share does not equal consumption.

And so it's certainly possible that in those high per capita areas, that the actual amount of units being used is greater than in some of the low per capita areas.

And so just to close my comments out, I just wanted to highlight that there is this utility in this market scanner data, I think for postmarket surveillance, because the data could be useful to refine and to focus the kind of questions that we need to be asking, about what makes these products attractive to those people that are using them.

And that the data could also be useful for surveillance activities to geographically target where we might be able
to focus in on that surveillance, when you're really looking for, at least initially it could be a very small group of people and so you want to maximize your resources and help find those individuals.

MR. HOLTZ: Thank you. Our next speaker is Dr. William Maier or Maier?

DR. MAIER: Maier.

MR. HOLTZ: Maier.

DR. MAIER: Yes.

MR. HOLTZ: Okay. Ph.D., M.P.H.

and he's Vice President of Epidemiology, Drug Safety, and Risk Management at REGISTRAT-MAPI, the industry's largest clinical research organization dedicated solely to real-world clinical research.

Dr. Maier has over 20 years of experience in drug development, in commercialization, in pharmaceutical companies in Europe and the United States.

He was previously Senior Director of Epidemiology at GlaxoSmithKline and Elan
Pharmaceuticals, and led research groups conducting observational research using registries, databases, chart reviews, and field research to support reimbursement, marketing, and drug safety investigations of pharmaceuticals throughout the world. He has worked on over 50 observational studies in several disease areas, including respiratory, neurology, psychiatry, autoimmune, cancer, endocrinology, cardiovascular, cerebrovascular, urology, opioid dependency, and vaccines. Dr. Maier?

DR. MAIER: Great. Okay, well, thank you very much. And thank you very much for inviting me to this, it's really been very interesting and I've really enjoyed a lot of the discussions. I don't have quite the background in tobacco that a lot of the other people do, mine is more in kind of product surveillance, you know, for pharmaceuticals. And there's some things that we can learn from that and
some things we can't really apply.

But there's one thing I wanted to show you and just talk a little bit from the kind of, what we've started here. And if you look at the very bottom of this biography, and I didn't know we were going to not have these, it says, European Network of Centers of Excellence in Pharmacal Visuals and in Pharmacal Epidemiology.

And I think it might be something for the FDA to think about, setting one of these up. I mean they could set one up obviously, for this purpose too.

But I think just for tobacco, and you've got all these people who are been involved with this for such a long time, and the NIH has already been funding a lot of this stuff, you've kind of already got something like this.

This is something that the European Medicine's Agency set up to get all of us together who are involved in Pharmacal
Epidemiology in Europe. And, you know, there's 30 different countries in Europe, and there's all these different centers and you never knew who it was.

And we got together in a room kind of like this, and we sat and we talked about, and they had four different agendas. What are the resources we have for doing postmarketing surveillance work?

What is the standards by which we would want people to generally work towards? So kind of like a transparency standard, that kind of stuff.

Is it easy? I would say it's not easy, but it is very useful. Now the thing about this particular one is that you can come if you're a researcher working at an institution or a company, but you can't come from a drug company. So drug companies can't be part of this network. So it's independent of drug companies.

So there's some things to learn
from that, that I think could be incorporated into this. I mean you've started a great process here, pulling all these people together, and maybe working towards something, using something like that could be a nice next step.

So I think you can see this. I can barely see it unfortunately, but I wanted to kind of think about this in its totality. Because the issue that I have found with all of this when I started to really look into it, is like there's lots, and lots, and lots of information and you just get overwhelmed really rapidly.

So my experience is more kind of working with companies and working with regulatory agencies, trying to figure out what kind of postmarketing surveillance could actually be done.

So ultimately it comes down to, can you do it? Okay, that's kind of postmarketing surveillance, and there's lots,
and lots of really great ideas, but if you can't do them, then it doesn't really matter.

And so, I try to help people figure out, well, what do regulatory agencies want and then regulatory agencies kind of figure out, well, what can actually be done.

So if we look at patterns of use as the first one, there's lots of population surveys going on in the United States now. And my guess is that they will continue to go on.

So companies could tap into that as a way of kind of like observing how their own products are being used. And I'm sure that that information is going to continue on the way it's going.

Now the big problems with those are, how representative are they really, and how frequently will they get done. So and again, that's something that can be negotiated as a condition of approval. So most of these things could be done as a condition of approval.
approval for a new product.

Impact of switching, well, I mean, switching studies can be done in the clinical setting for a limited point of view. But, when we think about postmarketing, it's probably current users.

Now there's going to be a big debate about what's a current user, right? Because people go on, and they go off, and they go off. But, you know, you start with a product and see how well you do.

It's not so difficult to do this probably in some situations because as we know, there are lots of user databases of people who are already using certain brands of tobacco and so on. So that could be tapped into for potential recruiting.

The only problem is that, that's only going to represent a sample of users. And so it may be that you need to go the extra mile and get one that's not a typical sample of users.
If you want to look and see what happens in bars on Saturday nights or something like that, that's where it's going to get challenging. It's going to be the breadth of what we can find out. But we can definitely do the switching studies.

Now the biomarkers and intermediate clinical endpoints. I mean I kind of made it really simple, like you can do a clinic study or you can do population-based screening.

Unfortunately, clinic studies cost a lot, and the big white elephant here is well, what are the actual endpoints that you should be looking at because there's thousands, right, thousands of endpoints.

So that's kind of a problem. But it occurred to me that, I was looking at kind of like well, what if there was a reasonable surrogate, kind of at pack years, right, which is a dose and duration thing.

Now people won't like this, but
I'm going to throw it out there anyway for people to start thinking about it. And that is, that if you look at Framingham which is the Framingham Heart Study, they have a nice little risk score, you can't get it online but there's plenty of papers that have been published, looking at the risk of cardiovascular disease in relation to pack years, duration of exposures, of dose and duration.

You can sort of work towards that as kind of population surrogate, if you will. So if you take the discussion that they had around Eclipse, all right, where they said, well, it has this level of exposure if it's smoked this way, but people actually smoke it that way, where they get a lot more exposure.

That kind of implied to me that you could kind of predict what people's smoking behavior would be fairly quickly, maybe within six months to a year, or maybe even less using a new product.
And you could take that and use that as a predictor of some type of like pack year surrogate, and then that pack year surrogate could like be used as a threshold for risk, if you see what I'm saying.

So in other words, the FDA would say well, we need a theoretical threshold in the population, and we're not going to have any products that are going to ever get to a point where you're going to have more than a 10-pack year or something like that.

It kind of falls apart when you start to put it into to fine a thing. But I think if you start to look at it that way, as a framework, it could work.

Health outcome and mortality.

Well, this is why I think working towards some sort of pack year standard, or some sort of intermediate surrogate that we already have established risk profiles for.

So you may remember we talked earlier about the whole lipid argument, right,
or high blood pressure is exactly the same argument, the two arguments are the same.

Which is that, you don't want to have high blood pressure because you're going to get a stroke, but we don't wait to figure out if you're going to have stroke, we just treat your high blood pressure.

So that's kind of the problem here. It's going to take us 20 or 30 years to figure out if you're going to get like, lung cancer, or maybe not so long to figure out if you're going to get heart disease and so on.

So anyway, to wrap it up. The last ones I think are pretty straightforward and frankly, I didn't quite understand the last question as it was being asked. But I think it kind of is, what's the framework by which this can all get done. So I leave it there.

MR. HOLTZ: All right. Thanks and we'll be sure to get back to other points that I rushed you through there. Our final member
of this panel is Mark Parascandola, did I get
that correct?

MR. PARASCANDOLA: Exactly right.

MR. HOLTZ: Who is an
Epidemiologist of the Tobacco Control Research
Branch of the U.S. National Cancer Institute.

He received his Ph.D. in
Philosophy of Science from Cambridge
University and his M.P.H. in Epidemiology from
the Johns Hopkins University School of Hygiene
and Public Health.

Dr. Parascandola also completed an
NCI Cancer Prevention Fellowship. He has
authored numerous published articles on
surveillance of new tobacco products,
epidemiologic methods, and the history of
tobacco control research and policy.

At the NCI he's involved in
developing and promoting funding initiatives
related to tobacco products and tobacco
control policy. Dr. Parascandola?

DR. PARASCANDOLA: Thank you.
Thank you all. I'm glad to be here and participate in this workshop. So I'm going to focus briefly in the time I have to, on briefly discussing our experience from some survey research we've done at NCI focused on novel tobacco products that are already on the market.

So in some ways this is a, I think related to what Dr. Delnevo was speaking about also. Although, our approach has been a little different.

So while the studies we've conducted over the past few years don't necessarily represent, I'd say the ideal model for postmarket research and surveillance, I think we can learn a lot from the early results we've received, and also from some of the methodological challenges we encounter.

And also, I don't want to suggest that the products that we're looking at here are actually modified risk products of course, but they were selected because of their
potential to be perceived by consumers as
modified risk products.

So several years ago we added
questions about potential modified risk, or
reduced exposure products to two national
surveys that are developed at NCI.

The Health Information National
Trend Survey we, in two waves in 2003 and
2005, we included a couple of questions on
novel tobacco products. That's a survey that
looks at health beliefs and behaviors among
the respondents.

And then also, in the Tobacco Use
Supplement to the current Population Survey in
2003, we had a question related to some of
these novel products. And we actually gave
some sample brand names of products that were
then on the market, they're not necessarily
all on the market now.

And asked people about their
awareness, use, that is had they tried one of
these products and also, interest in trying a
potentially reduced exposure, modified risk product.

And also not shown here, we did also add questions to a marketing survey conducted by the Forrester Company. And while that wasn't necessarily a representative sample of the entire population, it did allow us to look at some of the characteristics of people who are interested in these new products.

So basically, we found that the level of use and interest in these kinds of novel products varied by a range of factors, including demographics, age, gender, smoking status, whether someone's a current or former smoker, the amount of cigarettes they smoke, their degree of nicotine dependence, things like their attitudes towards new technology. And also their health concerns and beliefs.

And I just wanted to highlight a couple of the key findings here. One is that we found interest among current smokers in
this class of products was high, and more than
50 percent of smokers said they would be
interested or very interested in trying one of
these products.

And I had put the question up, but
basically we sort of had a hypothetical
question, if a product was introduced that was
marketed as potentially less harmful than a
conventional cigarette.

Also, we found in the HINTS Survey
that interest in these products was higher for
female, older, daily smokers, not currently
considering quitting, and those who view
themselves at higher risk for lung cancer.

So these were generally people who
were somewhat concerned about the health risks
of their smoking. But either were not
actually considering quitting at the moment.

In the Tobacco Use Supplement to
the current Population Survey, we found use
was associated with younger age, higher
smoking frequency, smoking a light brand of
cigarettes, a higher level of dependence, and a higher number of quit attempts.

So I should point out, trying to make sense of these results is actually quite complex. So one of the most important questions we have here is, whether people really perceive any of these products as less harmful than conventional cigarettes. And whether those perceptions about a product can influence their behavior and their interest in trying a product.

And I think in this regard the results we received were somewhat inconsistent. That is, we didn't get consistent information about a relationship between interest in the product, and quitting intentions or behavior, across these two studies. That is, they could be seen as conflicting.

And also, we found that interest in novel products is not necessarily associated with an explicit expectation of
risk reduction.

So that is, on the HINTS Study, we found that people who are interested in these novel products, that their interest was associated with a fatalistic attitude towards cancer risk. So that is, these are people who agreed with statements like, I can't do much to reduce my cancer risk.

So I guess the point I wanted to make is, trying to tease out how people are thinking about the comparative level of risk across different products is very complex.

And then trying to translate that into predicting how that's going to influence their behavior, in not just trying a novel product but actually becoming a regular user of it, is extremely complex at this level.

And I did have a final slide just listing some of the challenges that we faced, methodological challenges at this kind of survey research. But I guess we can get to those in the discussion. But I think these
are lessons to consider for future survey research on products out on the market.

MR. HOLTZ: Okay. Thank you very much. I guess one question that they kind of touched on, but what do you see, and the answer's probably both, but in what circumstances do you set up your expectations for postmarketing surveillance on a per-product basis?

Say okay, an applicant comes in, and you say, well, we're going to prove it if you do this kind of surveys. And what would you tell the FDA about well, we need to just set up national monitoring that's ongoing, that's monitoring all these products, so that we can have consistent, regular, and comparable data.

And then watch for what happens when a new product is introduced and then set targets for say, well, you've got to meet these, if we see X happening, the red flags you mentioned, then that would be a problem.
for your product based on this ongoing
national survey.

How would those two kinds of
individualized versus standardized
postmarketing surveillance fit into this kind
of system?

DR. DELNEVO: I think you need to
do both. I think we need to strengthen our
current surveillance infrastructure with the
surveys we already have going. I think we
need to insure that the longitudinal study has
all of the basics in there on day one, that
need to be there.

And then you're going to have the
smaller studies that are going to be tailored
to the specific new novel products that are
being introduced.

MR. HOLTZ: In the ongoing ones,
what would be the kinds of things that should
be in place, that don't already exist in the
national surveys that are being done on a
regular basis?
DR. DELNEVO: One of the things I think needs to be in there and I think in 2010, I think it got into the TUS, it got into the NHIS, it's in the NSDA, and that's brand. It think brand is important.

Users of tobacco products don't always know whether they're using a dissolvable, or a moist snuff, or a snus product, or a little cigar, or a cigarette, but they know what brand they're using.

And so that can be really useful and instrumental. And I think in 2010, all of the systems got that question in, at least for smokeless, and I think it's imperative that we insure that it continues to stay in there.

And in systems like BRFSS, which are going to provide data at the state level, but when you put all 50 states together, now we're talking huge sample sizes. We need to get that brand question in there as well.

MR. HOLTZ: Yes?

DR. PARASCANDOLA: Actually, I
would just say, I would agree that that's an
important thing to add. Although, I would add
one caveat that we found in our studies is
that, especially when we're trying, I think if
you ask smokers which brand they use, they'll
know, or tobacco users.

But we were also trying to ask
non-users, had they heard of one of these
products, would they be interested in trying
it? And I think there we found asking about
specific brands was not always very reliable.

Because people, they may've heard
of a similar brand name somewhere else, I
think Eclipse was the one example we had,
where we had an unusually large number of
people say they had heard of or tried Eclipse.

And we weren't sure if that was
really the product, or there's a chewing gum
called Eclipse or some other product out
there. So, I would just add that caveat.

DR. BORGERDING: I agree as well.

And actually, my opening comments I think

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communicated that. But the ongoing surveillance needs to be the backdrop.

And then for a particular MRTP, you would have specific information, control groups that allow you to link to that ongoing surveillance to give you the best quality of information.

In terms of some of the existing types of studies that go on or surveillance that goes on, if we look at the NHANES Study for example, it's exactly what you've brought up.

And that is, there's not enough brand-specific information to know what people have been using. There's certain categorization, but not very specific information about their tobacco product use.

On the biomarker side, there are a limited number of biomarkers, but they're not generally the ones that relate to tobacco use or the so-called Hoffman analytes.

In addition, that particular study
focuses on taking spot urine samples for example, for biomarker measurements. And there has to be consideration of when is it appropriate to use spot urine samples versus 24-hour urine samples.

So at the more granular level, there's a lot of technical issues to sort through. The answer to those technical questions depends upon the intended purpose. Once that's clearly stated, you can line these things up to sort of achieve the stated purpose.

MR. HOLTZ: Dr. Abrams, what do you think?

DR. ABRAMS: I largely agree. I do think though, we have to be realistic. The current surveys are very limited in some of what they can do to respond to rapid and emerging products.

Even to get some of those questions in takes a while because the bureaucracy and the way it's done. So I think
we have to also, in some senses be creative
about developing new methodologies and
methods.

The answer is, yes both. And the
standard surveys can be very helpful, but I do
think we need to put much more effort into
thinking about how to design that national
longitudinal survey, as Dr. Delnevo said, so
that we get it right.

And it's not so much just the
baseline, but it's thinking about how you
frame and conceptualize it, so that you can
build in some of these other creative ways to
do rapid monitoring, you know, sort of canary
in the mine early warning flags.

Combine this very carefully with
creative new informatics methodologies. The
commercial people are just using viral spread,
guerilla marketing, Facebook, internet-face
technologies.

And while we are starting to do
that, and there are clearly some questions
about reliability, validity, and sampling, we haven't nearly done enough of that at the level that would allow us to almost catch in real-time, the emergent and viral spread.

Much like you alluded to with the flu epidemic and what's going on, let's say in pharmacies. So I think we really haven't fully thought through how much these new tools could be used to supplement, inform, and triangulate to give us the best set of information to make the best decisions.

DR. MAIER: Yes, I mean I guess the only other thing I might add relative to what everybody else has said, is that it kind of depends on the product too, as to how it's going to worked.

Because I mean, you know, if we sort of think of it as just cigarettes and you can sort of ask people, that's one thing. But you're going to probably also want to know, usage characteristics in quite a bit of detail, at least initially. At least after
the thing comes up.

So my guess is that the FDA will have to require product specific things. And the other challenge you're going to have there I guess, is that there may be ones that are going to be done for the purposes of reducing risk or reducing exposure.

But there may be the same product I guess could even be out where there was no claim. Or a similar type of one by a much smaller manufacturer.

And that's where it's going to get really, really confusing to use kind of national surveys, because people are going to get pretty confused, pretty quick.

So you're going to have to have these kind of individuals surveys as well. And I think that the challenge will be, if you have a big manufacturer, that's one kind of infrastructure that can be maintained.

But what if you have hundreds of smaller manufacturers, how exactly are you

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going to do that? And you may want to 
collaborate them all together into some sort 
of cooperative study or something like that. 
Not necessarily government funded, but would 
require multiple people to contribute to.

MR. HOLTZ: What will be, do you 
think the role of the FDA in providing 
guidance about the design of individual 
surveys or other surveillance so that, I mean 
is there a need to have some sort of 
consistency even in those individual ones?

So that you can compare in some 
way results from one to another, or can they 
just be the manufacturer, the applicant just 
comes up with, we think this is the right way 
to track this particular product as a one-off?

DR. MAIER: I mean I guess I'll 
just follow on that one. The FDA ultimately 
sits in judgment of it, don't they? So if 
it's a condition of proving a new product, 
then they will decide, but they won't 
necessarily know because everybody will have
to be consulted, and there will have to a lot
of discussion about that.

I guess the other question is kind
of, what's the point of the information
anyway? That's the really hard thing to kind
of figure out here. You know, because you
think well, so you find out that people aren't
exactly using it the way that you said.

So then you require them to go out
and do some counter education or something
like that. So I think that's the other thing,
it's like what's going to happen afterwards?
I think that's not very well stated here.

I mean it's pretty straightforward
with the drug, you know, if it has a problem
that's unacceptable relative to the benefit
that you think the drug is supposed to do,
then you might take it away.

But, these aren't medical
products, these are recreational products. So
you have a different set of standards that you
might adhere.
MR. HOLTZ: Yes, Dr. Borgerding?

DR. BORGERDING: First of all I would hope and expect that the FDA would provide general guidance. But more importantly if I understand the Act correctly, if a modified risk tobacco product is approved, then the manufacturer has 60 days to provide their postmarket surveillance plan, including the principle investigator for review and approval.

So I don't think that there would be the situation, again if I'm reading it correctly, to where it would just be sort of a let's go do this study and hope they like it later. There would be dialogue around, is that the appropriate study to do before it's conducted.

MR. HOLTZ: Yes. What about -- Dr. Abrams, explain a little bit more about the red flags, the trigger kind of things, can you give us some examples of how this might work, how you would build it, and how you
would have a system, so that you aren't having
to think about oops, we need to do something
on an ad hoc basis?

DR. ABRAMS: Well, I think as you
said, the concept is easy to say, how you
operationalize it and do it in practice is
much more challenging.

But I think what we need is some
guiding principals, as I said before. Each
product is going to be unique and have it's
own set of concerns.

And so one way to approach this is
to insure that you convene if needed, perhaps
rapidly at an interdisciplinary small expert
panel to look at what are the concerns,
unintended consequences, because no one person
can be expert to anticipate everything from
bioexposure to epidemiology.

So you need a little bit of a
mechanism for knowledge synthesis and rapid
consensus building of expert groups, as one
part of looking for red flags.
And I think there are some fairly obvious things that are easy to say, you know, it could be clear for example, that somebody markets a product with a reduced risk claim, let's say a dissolvable.

And it's very clear from some early monitoring, let's say with more intensive say internet, or smartphone, real-time monitoring, that all this is doing is increasing exposure, because there's no reduction in combustible cigarette use, and there's increased use of this product.

And you might be able to for example, set a criterion that says, if 80 percent of the population using it is using it in this pattern, the scaled-up likely public health damage is of sufficient concern to put up a red flag and say, if that happens, if you see that happening this product is going to be withdrawn from the market.

So it's a little bit of a hypothetical, but it's an easy one to sort of,
but I think we need some principles and some
guidelines and some ways to approach the
problem.

DR. PARASCANDOLA: Well then, yes,
I would agree with that, I guess the other
thing I would add is one of the challenges we
face too, with some of the existing survey
mechanisms is we don't have an ability to
track behavior over time.

And so we can, in different waves
of a survey, we can know how many people have
tried a product or are interested in it, but
we don't really understand how their tobacco
use behavior develops over time.

So our people switching from their
usual brand to some novel brand, are they just
sort of trying it as an experiment, and then
going back to their usual brand. And so I
think that kind of tracking over time would be
essential, somehow. Maybe the longitudinal
study would be one way to do that.

MR. HOLTZ: Dr. Delnevo, you had
mentioned some of the commercial market survey
data gathering that's going on now, how is
that useful information in this process? What
is available?

Are there things that are being
done on a proprietary basis that the FDA might
want to say, hey, we want to see? We want to
see all of this data in order to track what's
happening in the marketplace?

DR. DELNEVO: Right. So the
example I gave was the Nielsen scanner data,
and there's another company that does data
collection similar to Nielsen. It's not
survey data, it's actually UPC codes that are
scanned at point of purchase.

But the UPC codes are coded with
very detailed characteristics of the product.
So researchers can look at that and kind of
isolate what factors are driving the growth in
whatever. So you could look at for example,
with smokeless tobacco, the cut of smokeless
tobacco. Is it fine cut? Is it straight cut?
There's different, some of them are stronger with regards to nicotine based on the cut, so those are things that you could actually look at with regard to that. And they are proprietary data sets, but they're available for purchase by the researchers.

MR. HOLTZ: So is that something that you routinely think, I mean, is that something that the FDA should want to see all the time, whenever a new product is introduced?

DR. DELNEVO: I would think so, yes. I mean and you can get the data segmented in as smaller time chunks as you want.

You could purchase it in one-month block, quarterly, half-year, year, so I mean you could actually track how a product is doing relative to, both in terms of volume and market share, you know, on very small time frames, if need be.

MR. HOLTZ: Do you think, can we
get to this, obviously in this, when we look
at surveillance and studies of what people are
doing in the real world, there are all kinds
of things where you could do smaller studies
that are very short-term.

And then you've got these big
national surveys or one-off things, that go to
a journal and it might be really good data,
but it takes a long time to see it.

Can we get to a point in this area
where there is something more like the
political tracking polls, where we know
almost, if you want to, day-by-day where key
demographics are going. And get to that level
of saying, oh, we can predict what's happening
out there based on this ongoing regular
surveillance?

DR. ABRAMS: I would say, yes we
should strive for that, and it's very doable
in this day and age.

It's sort of what I was eluding to
in the fact that in other areas this is being
done, particularly in entrepreneurial and
commmercial places where, you know, that's life
and death for a company, trying to sell and
increase consumer demand for a product. So I
think that's going to be critical to build
these systems.

And the other pieces I think we
have to be more flexible about, accepting,
moving beyond the so-called gold standard of
the randomized clinical trial with a classic
control group.

There are now very rigorous
methodologies that answer the right question
with the right methodology. And there are
times when randomized trials, actually is the
wrong methodology to answer a particular
question.

So I think there are also now
sampling technologies and even borrowing from
engineering, there are methodologies that
involve how you do continuous quality
improvement in very rapid iterative cycles to
improve a product or to change the consumer perceptions of the product, very systematic.

And these kinds of methodologies and the statistics that go behind them are evolving, but they're getting to the point that they could be very, very useful for these particular kinds of applications.

MR. HOLTZ: Yes, got a question, comment from one of the other panelists.

DR. SHIFFMAN: Saul Shiffman. I was going to comment on both of these things. Well, first let's address the current federal surveys. And the reality is they're way too slow. They tell you what was happening a couple of years ago and that's way too late. So we need other mechanisms. And there are some administrative issues because of OMB clearance, et cetera. So that's something for FDA to struggle with.

But these data sets are very rich. And I was going to comment particularly on Nielsen, that you can get not only data about
products, which tell you a product is being purchased or not.

But you can know what things were purchased at the same time. So for example, they do a market basket analysis where, you know, that the person who just purchased this new product also purchased cigarettes.

And some of the vendors have longitudinal data. Now mind you, this is household really, because the person could be buying for a spouse, or a kid, or parent, whatever. But you could potentially for example, track that as this new product is being purchased, prior purchases of cigarettes are declining or staying the same.

So while they don't have the perfection of an individual, perfectly representative, longitudinal study, they're very fast. And again, just by linking the data in different ways they can be extremely informative. And again, not just about total volume or market share, but co-purchase and...
changes over time.

DR. MAIER: Could I make a comment about that?

MR. HOLTZ: Yes.

DR. MAIER: This is really fascinating and I was really interested to learn, but I don't know if that tells us as much about modified risk as we would like. I mean, and that's the problem with quick surveys. I mean we can probably get a lot more data, but the question is, what will the information about modified risk, because that seems to be the thing.

So I think you can learn about, you know, risky behaviors in that context. Or you can see that certain groups of people who shouldn't be getting it, maybe are.

Although, I think even with market data, that's really challenging. The challenge is linking an exposure to an outcome in this setting. That's the real hard thing, and so that's kind of where I think the rubber
is going to meet the road here.

And so, you know, if it's possible
to get back a track utilization and then
somehow, you know, follow somebody over time
in a much more easy way, through electronic
linking, or surveys, stuff like that, with the
tools that we have or even communities, like
social networks. I think that is what's going
to be the defining factor here.

Because that's kind of what we
really want to know is, well, did it make any
difference in terms of the individual risk,
and also at the population level too, but you
need to have that link somewhere.

DR. ABRAMS: Just to build on
that, you know, I think again, one of the
challenges is, we have experts in various
silos like epidemiology, even now experts with
rapid Facebook type viral spread and guerilla
marketing.

And we don't put them together, so
that we can maximize getting from what might
be a highly biased self-selected sample of early current users, which does tell you something.

And tracking them over time let's say, because it's much more important to look at their actual behavior and as we said, you know, risk, exposure, and harm reduction are very separate things and aren't often connected. How do you directly measure what you need to?

But then how can you do that within the context of preserving that you've drawn them from samples where you know something about the context, the generalizability, and where they came from.

So that you're combining the best of several disciplines, and several worlds in order to get to exactly what you're saying, because we can just stop short of that with what we talked about earlier.

Again, I think it can be done in interdisciplinary teams fairly quickly, but
you have to have the sort of leading experts
in each of those areas to take advantage of
things that, you know, each person's an expert
in one thing, and they don't know how to link
it to the other thing.

So I'd say that's another approach
that is new and innovative, but is necessary
to respond to this particular kind of unique
challenge.

DR. BORGERDING: The discussion
has in part been around, based on your
question, how do sort of get real-time
information, and a lot of the tools that are
available, and the discussion has focused a
lot on product use.

My response to your earlier
question would be, it'll take different
amounts of time for different types of
information.

For example, the type of
information that was being discussed, while it
may tell you something about use, doesn't tell
you anything about tobacco product use history.

So part of it will be discerning what information is important, what the objectives of the program are, and then putting the pieces together, as has been said by the panel, in a meaningful way.

While some studies might be quite long and have quite a time constant, sort of like a raft on a river rather than a kayak, that doesn't mean that without information, and it may not be the appropriate thing. But the key will be what do we want to be able to monitor. What do we want to be able to address, and probably one size won't fit all in terms of these different tools.

MR. HOLTZ: Does it sound like, in terms of what adequate postmarket surveillance and studies would be, it's not going to be something simple where you say, do this study, follow-up study and get back to us.

It's going to be, would you think...
that the FDA needs to look at something that's
more comprehensive, multifaceted, and say,
here are the range of activities that need to
go into your plan for figuring out what
happens once the product gets out into the
real world?

DR. PARASCANDOLA: Yes, I would
agree with, I think it's going to have to be,
yes more of a system type approach than, you
know, there isn't going to be a single
methodology that's going to answer all these
questions.

And so, I think Saul's point was
important about the limitations of the
national surveys and that. But I think these
different methodologies may have things to
contribute at different levels.

So there is a need for ongoing
national surveillance, and I think there's
certainly room to enhance the national
surveillance capabilities we have for tracking
all tobacco products, not just potentially
modified risk products.

But at the same time, yes there is also a need for more targeted research methods that address specific changes in the market or new products as they come out.

MR. HOLTZ: What do you think the FDA needs to look at in terms of who you look at? I mean, we keep hearing over, and over again that there are different types of tobacco users or people who might become tobacco users, there is youth, and there are different kinds of youth.

There are goodie goodies, and there are rebels, and they have different characteristics, there is income, and education, there is women of reproductive age.

What kinds of, in the surveillance what are some of the key demographics, the types of people that need to be included, so that you know that you are looking in the right places and not missing important changes that may be really important in very small
percentage of the total population?

DR. DELNEVO: Well, classic behavioral surveillance has a population focus. So by it's very nature, if it's nationally representative you are hitting all of those populations, which is why I think that we need to look at what's available.

And strengthen, you know, the basic foundation of what we have, taking into consideration that we're going to need also these very targeted specific studies with questions that are tailored to the products that you're looking at.

But for example, when we look in the Surgeon General reports, when we look at the epidemiology of tobacco use, we don't just look at one survey. We look at all the federal, and national, and state level surveys that are available and we triangulate across them.

Because each study in and of itself has it's own inherent strengths and
weaknesses. But when we put them all together we expect to see consistency, to see if that is in fact, what might be going on. So all of the studies are important, there's just different aspects to them.

DR. ABRAMS: Again, I think we need some guiding principles here to inform us where to look and where to prioritize. And one sort of obvious set of thoughts about that is, if you want to make the biggest public health impact at the population level in saving lives according to the mission of FDA.

If you sort of work backwards from that ultimate challenge, what are the pathways that lead most rapidly and efficiently to that? I would guess you would come up with some of the obvious ones.

Like there's huge health disparities by socioeconomic status, and it's almost like smoking is a problem of the low SES groups.

So if you don't make a dent in
some kind of modified risk reduce harm strategy that will make a huge difference for, let's say the low-income, high-prevalent smokers, or even the states with the highest smoking rates, Kentucky is 30 some percent versus less than 15 percent in California.

There are ways to target and prioritize in order to drive the public health impact mission. So that would be one potential guiding principle, is to look very carefully at differences in groups like the SES, I would argue.

And I would also argue based on what Michele Bloch and others said, that young adults is a critical population. So your roughly 18 to 30-year-olds.

Because if you can get them to stop in that long duration of exposure thing or reduce that dramatically, it's going to make a big difference in the ultimate public health outcome.

So we could probably develop some
nice algorithms there and begin to use those
to weight and prioritize, essentially where we
should be looking and where we should be
putting a little more resources and energy,
when we look at differential impact of
different types of reduced harm products by
sub-populations.

DR. MAIER: Yes, I mean I think
it's very useful for us to understand which
groups of people are using it, but it also
kind of gets back to the same question as,
what are you going to do with the information
once you have it?

Because I mean we were having a
discussion at lunch, and we were saying, who's
going to use new products. And I said, oh,
you know, if it's reduced risk, it's probably
going to be predominantly more female because
they're more interested in health things
relative to men.

And actually that's what this
survey would kind of suggest. So that's good,
but then the question is, what about the people who are left behind? What should you be doing about that?

And at the moment, you know, you might do nothing, right? And that's probably not where people are going to feel very comfortable.

So I think that's the challenge.

There's public health promotion and then there's regulation of products. And they kind of overlap, but they don't explicitly overlap because of the kind of product that this is.

I mean if I, as a certain age group of person want to do something, then I kind of want to do it, right. And if it's legal then I should be allowed to.

So that's the thing that kind of comes in conflict with all this information we're trying to collect too. And that is, that people may not really want to get it, you know, it's one thing if you're sick. It's another thing if you feel fine. So, I think
that's our big challenge here.

DR. ABRAMS: Can I just add two comments. You know, one other thing is there are unintended consequences of just how we go about doing this. I think we have to be very careful in the fact that whatever is done and mandated by FDA, will be sort of judged in the court of public opinion.

And one of the things we've learned over the years I think is, you know, consider the source. And if the credibility of FDA and the sources of this information start looking questionable at some point, it weakens the whole system and the whole process.

So I think another guiding principle here is above all, to be really sure that what we're doing has some public credibility, and has the transparency and honesty that was talked about at one of the earlier sessions.

You know, the truth, the whole
truth, and nothing but the truth, kind of
comments. So I think we've got to keep that
in mind as well, in terms of a context of how
we do this kind of work.

MR. HOLTZ: What do you think
would threaten the credibility?

DR. ABRAMS: Well, certainly we've
already talked about some of the things that
might threaten it. I guess the best example
of this is, the apparently well meaning, you
know, low tar, low nicotine cigarette.

Where the scientists and the data
were not in, but everybody said, let's try it
and, you know, let's go ahead and do it and
we've seen some pretty terrible consequences
which threaten the credibility of, can the
government protect us?

You know, the obesity epidemic.

Were we all sleeping while we got to this
horrendous state. What happened in the last
25 years, when we didn't have those early
warning canary in the mine flags? So that
sort of threatens the credibility of the whole, you know, public health, scientific monitoring enterprise.

MR. HOLTZ: Yes, do you have something?

DR. MAIER: Yes, I mean you can go a variety of different ways, and I was thinking that what would enhance the credibility of whatever we decide to do or whatever, it's just the transparency and the way in which it gets done.

And, you know, if you make it more transparent and you get more information out there, it's usually better. Now the downside of that is that there's a tremendous amount of information out there already.

And as we know, it gets very confusing very quickly to figure out what's actually going on. So that will be the other big challenge is, how we maintain communication or how communication is maintained.
But, you know, the FDA actually does an excellent job when it comes down to certain things around drugs. I mean the website is great.

If you go look at the drug website, it's got everything. And everybody reads it everywhere, all over the world, everybody does. So that's a pretty good way of starting, frankly, just do what you've already done.

DR. BORGERDING: I think part of the concept of honesty, transparency, and scientific credibility is acknowledging, given the complexity of what we're talking about, whatever happens to begin with is a starting point.

We'll learn from that, hopefully. We'll refine it through this collective process over time. But to think that something this complex can be thought out and implemented perfectly from the very beginning, is perhaps not realistic.
So I think part of the public perception, part of the transparency issue is setting the proper framework for the fact that it's an evolving process too.

MR. HOLTZ: What is, we've talked about some of the social marketing and peer-to-peer communication that goes on that may or may not be influenced by the, officially whatever the applicant provides, says this is our marketing plan, this is how the product is going to look.

And then it gets out, in what ways, or what do you think the FDA should do in terms of keeping an eye on those things that appear to be outside of the control of the applicant?

DR. ABRAMS: I think it's essential, we have to monitor new media, social media, and see it as probably one of the most powerful 21st Century ways of communicating. And so to me that's a tool and an instrument, as well as a phenomenon that we
have to stay on top of.

And I mean I would argue that what
the viral spread and the social norms of how
fads, fashions either rise and fall rapidly or
take hold and become more permanent, is a good
sort of analogy, to sort of Rogers' Diffusion
of Innovation issues for new products, say
with reduced harm.

But I'd also be somewhat
skeptical, you know, there's a lot of emerging
evidence now that companies are
surreptitiously using guerilla marketing and
essentially having people, where it's not
really clear that they're being paid or
promoted by an industry, to be the sort of
nodes of viral spread who make that process
take off.

And who apparently are the
consumers, but aren't. So I think all of
that, you know, it does become very relevant
to how is this product spread.

Again, I think e-cigarettes is an
interesting example. Because they haven't
generally been marketed in traditional mass
media ways and yet, you know, we have a survey
that roughly 50 percent of the population is
aware of them, and roughly 12 percent of the
population have used them at some point in the
last six years.

And roughly four to seven percent
of the population have used one in the last 30
days, if they are current smokers. And if
they're planning to quit in the next six
months, they're three times more likely to be
using an e-cigarette in the last 30 days.

So those are interesting
information that sort of fits into this.
Who's telling them? How are they knowing?
How is this all being communicated?

You can just look at Twitter and
some of the blogs and other things, and this
is all happening. It's critical because
that's what influencing norms and behavior,
and ultimately will affect the public health
impact.

So I can't see any way that we shouldn't be taking a lot of resources to understand and develop ways to use these tools to our benefit as part of the tracking system we have to put in place.

DR. PARASCANDOLA: Yes, I think that's, I agree it is very important. I think when we talk about it's important to understand how people use the product when it's a novel product, not just in kind of a laboratory experimental setting but also, how it's impacting the real world.

And so social media is obviously an important part of that, since it is how many consumers may get information or exchange information about a new product through those means.

So I think it's an essential part of understanding the impact of the product in the actual population. You know, there are studies that have looked at some of these
novel products and how information is
exchanged through You Tube, and Facebook, and
other social media and I would say that's an
essential piece.

MR. HOLTZ: Yes. Do the
applicants in the approval need to be held
accountable for things that may be out of
their control? Where you say, and
particularly if the premarketing testing was
done right and you saw that in test markets
certain things started to happen in terms of
social marketing, say, well, if we start
seeing, as far as one of your red flags.

If we start seeing some viral
conversations going on out there, even if you
disclaim any connection with this, then there
are going to have to be corrective actions
that you have to take in order to maintain
your approval. Should applicants be held
accountable in some way for correcting things
that just happen?

DR. ABRAMS: I'd say yes.
MR. HOLTZ: Yes.

DR. ABRAMS: On some level, the simple answer would be yes. Because it's irrelevant how it gets out there, if it's spreading and we think it's going to damage public health and go in the wrong direction, it's cause for concern and possibly action.

I don't know if this is a good analogy, I haven't thought it through, this is just off the top of my head. But it was okay to sell, you know, Ford Explorers with Firestone Tires, as long as the information wasn't out there that there was an excess risk beyond an acceptable level.

As soon as it became aware and that was really no fault of either Firestone or Ford, but at some point we said, hey, too many people are flipping over and dying. We've got to take action and we did. And they voluntarily removed them from the market place because that combination appeared to be more lethal than was acceptable to society.
Somehow that doesn't happen with products that have to do with tobacco. But I would say again, when the public health is endangered given the mandate of the FDA to protect the public health and reduce the harms, it doesn't matter.

MR. HOLTZ: And does food regulation offer again, a scenario where contamination, you know, in Oregon we just had a bunch of strawberries contaminated by deer droppings, that certainly wasn't really the fault of somebody, and yet the industry had to take action --

DR. ABRAMS: Yes, government just has to say, oh dear, I'm terribly sorry, but we have to take those off the market.

DR. BORGERDING: My response would be, I don't think that it's an issue of accountability, per se, it's an issue of what information do we think we need, and what might happen.

The scenario that you put forward,
the viral concepts and so on, I would suggest, may argue for what Dr. Shiffman was suggesting earlier, which is the concept of a test market.

If you want an early read because you have some concern about a particular possibility, then how best to probe that possibility, and so it's not a matter of accountability, per se. It's a matter of thinking through what might happen, having the plan to address that and finding a way to do it.

MR. HOLTZ: Go ahead.

DR. DELNEVO: I was going to say, that since you brought that up, you know, one of the things I've been thinking, after listening to the last panel talking about consumer perceptions, and issues with the industry not wanting to have someone else doing their perception studies because of trade secrets and what not about the product, is maybe there needs to be step between
premarket and postmarket.

And there needs to be this kind of
test market piece in between the two, where we
can actually have independent evaluations of
consumer perceptions, the issue about should
children be part of the consumers.

How do you define consumers?

Well, kids are consumers. They are. And I
said before, there was 84 Camel snus users in
the NSDA, one out five of them were under the
age of 18.

So they're using the products. I
can understand not wanting to do the kind
premarket testing with them, but if you
inserted a step in between the pre and the
post in this test market phase, before
something could be rolled out with messaging,
I think some of the concerns could be
addressed in that, in that particular step.

DR. BORGERDING: If I may, in our
dialogue before lunch I guess it was, my
initial reaction when I heard the comment was,
postmarket requirements are that we would report annually on the results that are obtained against the postmarket surveillance plan.

So in principle, if you're reporting annually that's almost like a test market, other than it's not finite in geography. So again, it's something that needs to be discerned, but is it a question of finite geography or finite time.

But there is a way to have intermediate information, the question is how rapidly can you get it. And how rapidly do you need it.

DR. MCAFEE: Tim McAfee, CDC. I just wanted to respond to a couple of ideas that are batting around, and I'll just go immediately with that one.

I think one of the original concerns that was raised about the idea of doing test markets, was contamination. It was like, ooh, we'd get these ideas out, that
would go beyond the test market.

Well, let's stop and think for a minute about what we're talking about. What you're basically saying is that we'd do a national experiment with and again, it's not the product. We're not talking really about testing new products mostly, what we're talking about is claims.

A government sanctioned claim that something is lower risk. And some of this is going to be for stuff that's already there, I mean a big issue is going to be existing smokeless products that don't have 55 people, but have millions of people.

So it's going to be hard if you do that in a national situation for several, just for doing it, even if we all wanted to put the genie back in the bottle, it'll be hard to do.

But I think another issue that is raised around this is, even if we are collecting data, it's the industry, FDA, and other parties are carefully going to have to
think through, how are we going to act if, so
we find a red flag.

   There's a lot of history,
   certainly even with other industries, in
   pharma, in the food industry, I think it's
   pretty unlikely that this is going to be as
   straightforward as deer droppings in
   strawberries.

   And how are we going to, in a
   situation where the industry is going to be
   perhaps highly incented to want to keep that
   claim on, how will we set up processes where
   we don't end up in litigation around it, or
   having to go through years of activity?

   I think we're going to have some
   frank discussions about, I mean just to give
   one final example around this, let's look at
   what happened when the FDA took, light, low,
   and mild characterizations off.

   And as Pam Ling presented, what
   the actual behavior was, is it the industry
   gave retailers, and did advertisements that
taught consumers how to make a transition, and
to understand which product, so to counter-
veil the public health effect, and what we've
seen is no public health effect.

That there hasn't been, people are
still smoking the same brand, they're just
doing it based on colors. So we're going to
have to get down at a deeper level I think, if
particularly this idea, oh, we'll just wait
until postmarket surveillance.

Even if we can get over these
problems of, how you would set up the
surveillance and we can agree on the things,
we also have to deal with the issues of how we
would set up something so that industry and
FDA, et cetera, would have the capacity to
rapidly respond, to change the messaging, if
necessary to withdraw the characterization.

And it'll be really hard to put
the genie back in the bottle, if we want to.
And maybe we won't, but if we needed to, how
would we do it?
DR. MAIER: Yes, I mean just to kind of build on that too, I mean it's really interesting if you go on You Tube and you type in Marlboro, what you will see is amazing, actually.

And I think the fact is that it's really hard to control a message now. Nobody really owns the message anymore. You know, we were talking about, what happens when you get a symptom, right.

Any symptom of any kind of thing, you run to the internet immediately and you begin researching like crazy. And the other thing that happens is if there's nothing about your disease, you look to build a community around that.

So I think we have to assume that the moment that you start talking about this idea, it's going to be zipping through, you know, society and new communities will be forming, and companies who've marketed the thing won't have any control over that at all.
So we have to kind assume that that will happen. And say, if we assume that that will happen, what does that mean in terms of what we will allow to get done. Because it's going to happen very fast.

DR. SHIFFMAN: Can I, Saul Shiffman, just to comment on that. There is an analogy which is that the FDA on the drug side has been very concerned about abuse of prescription medications, primarily opiates.

And in that instance the FDA looks at the result, not who caused it. So for example, sponsors are trying to develop abuse resistant formulations, but the users, and ab users are incredibly creative.

So within days of a drug being released, people are saying, you know, if you just take five of them it doesn't do anything. But if you grind it up and then put it in vinegar, and FDA doesn't say well, that's not their fault. The FDA says, look sponsor, your drug is creating a problem, figure out how to
fix it. And I think we have to take the same attitude here.

I think you're absolutely right, that people will form these communities, including figuring out how to possibly subvert the risk reducing aspects of new products.

You know, perhaps one can't do that with smokeless or snus, but if you put out something that's more complicated, people figure out how to get a better hit off it or something.

And I don't think we can say, let's assume the sponsor put it out there in good faith, whether they put it out there in good faith or not, if it creates a public health problem, it becomes something for all of us to fix. So in answer to the question of can you hold the sponsor accountable, I would say, yes we're looking at the result, not the intent.

MS. SNEEGAS: Karla Sneegas with the National Tobacco Control Network. It's
not if they are doing it, they are doing that now.

And I didn't include this in my remarks, but we have data from when the snus products were test marketed in central Indiana, some of the comments from young people of how many snus products they had to use together, in order to get the same jolt that they were looking for. So it's not an if, it's already happening.

MR. HOLTZ: And how did you find out that that was happening?

MS. SNEEGAS: We started searching the internet. We do runs on You Tube. And then we have all of our local coalitions. We have a network of local coalitions across the state. We teach them how to look for these things and then report them back to us.

MR. HOLTZ: So when an applicant comes to the FDA as part of the postmarketing surveillance plan, should monitoring internet activity and these other things be specified?
MS. SNEEGAS: Absolutely, absolutely. And looking at what they're doing with the product that has nothing to do with maybe even how the product, what the product was developed for. Putting it between their toes to get a, you know, we've found comments of snus products being used by teenagers during school hours, they put it between their toes so that no one will see it.

That dissolvable products are great to hide, principals, superintendents, teachers have no idea what they are. They don't go into convenience stores. They don't watch this type of thing. They don't know what it is, so you can get away with hiding these products for a long time.

MR. HOLTZ: We've talked about a lot of things that could be done and of course, it's not for free. Everything that you add say, well, we require this, this, and this, and this, and this, means it's going to be tougher, more expensive to introduce a new
product.

If a product comes along and you think, you know, this actually, it's gone through those earlier stages, and somehow managed to demonstrate that this might be a good thing for reducing harm to individuals and to populations, how do you factor that then into deciding, how much surveillance to ask for afterwards?

Is there a tension between knowing everything, and delaying the introduction of a product that might help people move away from the more damaging products?

DR. MAIER: Yes, I mean I would agree with you and I think one of the things that we were talking about was, how do we control social media? And we can't control social media.

And so, because we can't do that, I mean there's only certain things that we can do, you know, and so, I think what the regulatory agencies and the companies will
have to do is work together to be like partners, in a way that they may not have traditionally been partners.

Because they're going to have to think about, okay how can we be as open and transparent as possible? Because it's not going to be possible for small manufacturers who can legally develop these products, to do the kind of things that a bigger company could do.

And so in terms of fairness, the FDA is going to have to come up with different types of strategies for different types of products, I would say, and different types of manufacturers.

Because they do have that, I mean I don't know exactly what their responsibilities are, but I kind of understand that as being kind of part of their mandate too.

DR. BORGERDING: I think the simple answer is, yes, I mean that clearly,
we're hearing a range of views about what may be important.

I believe Dr. Abrams said it earlier, but in simple terms for postmarket surveillance, you can monitor intended consequences and unintended consequences. Having a dialogue, and even having guidance and regulation from the FDA about what types of things are important in each of those categories, will be critical.

If we have just a research agenda that's all encompassing, there won't be any incentive to actually have modified risk tobacco products, and in my view we'll have a very important opportunity missed.

So it's critically important to consider all these things. To try and discern which ones are most important and to your question really, in some ways, which ones are most cost effective.

MR. HOLTZ: Okay. We're getting close to the end of our time here. So let's
each weigh in again with either a summary or
touching on a point we've missed. Dr. Abrams?

DR. ABRAMS: I don't think there's
much more to say. Perhaps we know it's
complex, but if we think it through carefully
and use different perspectives, the industry
perspective, the research/academic
perspective, the regulatory perspective, and
make sure that that is involved in the
knowledge synthesis that leads to the ultimate
decision.

I think that's the best safeguard
we have that we will catch as many of the
dangerous red flags early enough, but we're
not going to be perfect at this and we're not
going to do it perfectly.

And probably my biggest worry is
that any message about accepting reduced harm
products could encourage kids to start using.
There's a little bit of a trend in the
HIV/AIDS area toward this.

That as soon as the drugs were
developed, the combination drugs that turned AIDS from a death sentence to a chronic disease management, there's a bit of an up-tick in, you know, young people being less concerned with risky sex, et cetera.

So there are some unintended consequences that have to do with longer-term feedback loops, that our brains when we think linearly and short-term, which we're programmed to do even at the highest levels, we'll miss.

And I think maybe that's where we've got to think very carefully about unintended consequences that actually may happen long-term. And I don't know how we get to the place where we can find a red flag that will tell us where they are way earlier than like what happened with the low tar, low nicotine cigarette debacle.

So I don't know exactly how to do that, but I think it requires perhaps the precautionary principle which was used

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earlier. That the ultimate red flag is when in doubt, you know, don't approve this and protect the public's health in a fairly conservative way. So I'm not so sure that we can just sit here and say the status quo is unacceptable.

Maybe I think product regulation, which is not the topic here, like reducing the level of nicotine in cigarettes might be the single best way to proceed, rather than somehow get the message out to the public that we're going to have a whole bunch of reduced harm products, which might encourage people to just keep using and experimenting.

You know, as Michele Bloch said, you know, people look for reassurance and they're vulnerable because their brains are hooked on nicotine, and so you give them anything else to say, oh, there's a little bit of reduced harm here, maybe it'll keep them smoking. And that would be one of my big concerns, how do we monitor that and make sure
they aren't long-term unintended consequences.

MR. HOLTZ: Dr. Borgerding?

DR. BORGERDING: Throughout my career I have found that having diverse opinions makes for a stronger end product. And throughout both my career and my lifetime, there's been an adversarial relationship between tobacco control, government, and the tobacco industry.

And I was very pleased today to see that there actually is an opportunity within a frame work to work together towards an objective of reducing the risk of tobacco product use, so I was very encouraged by that and again, thank you for the opportunity to be here.

MR. HOLTZ: Okay. Dr. Delnevo?

DR. DELNEVO: David said it. I said it in the beginning of my comments, that whatever we end up with for a postmarket surveillance is going to be complex.

And so, I think there is a couple
of things we need to kind of start with. And that is, cataloging what's available, finding out how we can strengthen what is already available to us and leveraging it.

And that goes beyond the government surveys, the academic communities collecting data on their own, and I think we need to kind of catalogue and find out what's there, so that we can maximize resources.

I also think that we need to innovate on our methods. And that we need to look at innovative ways to collect data, you know, I brought up the issue of looking at the needle in the haystack.

But if we took this longitudinal study and found ways to isolate those potential new adopters of the product, and use things like responded-driven sampling which is used for hard to reach populations, can that type of sampling methodology be extrapolated to something like this. I think we need to look at those things.
And the last point I want to make, this talk about social media and e-health, reminds me that, are there tobacco products on the market currently with explicit health claims of reduced risk? No.

Are there products on the market currently with implicit health claims? And I think there are. If you just go on Google and do a search on snus, someone who's considering adopting snus will find links that talks about the Swedish Experience, and the lower nitrosamine levels, and the pasteurization of the product.

And so people are walking away with, I think potentially impressions of reduced harm already, and so there may be an opportunity to start looking at those particular groups now, and look at consumer perceptions already, of products that may have not explicit, but implicit sorts of health related claims associated with the products.

MR. HOLTZ: Dr. Maier?
DR. MAIER: The only other thing I wanted to add was, I think that the goal seems to be admirable, that is to reduce the risk associated with these things.

The only thing is that we are going to make a lot of mistakes. And so, mistakes are just going to be made. You know, the low tar thing is considered to be a mistake now, and maybe the mistake was, you know, it got everything done really quickly. I mean it'll take a little while to figure out what the actual biggest part of that mistake was. But I can assure that in the future the mistakes are going to be made in this same process.

So the real challenge will be trying to establish a reasonably flexible framework, whereby you kind of understand things, and when you start to sense that you've made a mistake, you can kind of go back and change it.

And again, that's actually within
the context of the way in which the FDA already operates. So it's not really that big of a deal, it's just kind getting our head around this new way of thinking about it, in this particular product area.

MR. HOLTZ: Dr. Parascandola?

DR. PARASCANDOLA: So it sounds like there is a lot of potential for some creative use of some of our existing methodologies and data sets.

But I think at the same time, obviously we've all recognized this is extremely complex, and so we don't have at the moment, I think a sufficient existing surveillance infrastructure to provide the kind of ongoing monitoring you need of changes in products and the market.

And, you know, we really need a kind of diverse range of methodologies. And I think one area we didn't to as much, is tracking the actual health impact, you know, exposure and health impact of these products.
And that's much more complex and costly as well.

And so, I think because of the complexity factors, I think we can't depend too much on the postmarket surveillance to allow us to sort of provide all the corrective action. We need to do as much as we can early on in the process. Hopefully premarket, because otherwise we may be too late in the process.

MR. HOLTZ: All right. Thank you very much. Thank you to everybody on all the panels but we're not quite done yet because -

(Applause)

MR. HOLTZ: I think we've a closing comment from Dr. Ashley. Yes, I think if you stand, you can either stand there or sit here.

DR. ASHLEY: All right. Either one will work for me. I think I'll sit here.

MR. HOLTZ: Okay, then you'll be on camera.
DR. ASHLEY: I'm not going to look as good as you did up here. When I was in college I had a professor named Dr. Leon Mandel, and one of the things I heard him say was that, you can tell the quality of a college education not by the number of books someone reads while they're in college, but the number of books they read after they've graduated from college.

And that makes a lot of sense to me. I mean the basic message is, does a college education bring about the desire in a student to learn, even after they leave.

And my thoughts on this is a little bit along those lines. One of the things I hope, I think we had some incredible discussions here over the last two days.

One of the things I really hope is that this will spur even more discussions. And to me one of the, what I believe will be a real tell tale sign of this is if these discussions go on and we continue to learn
from each other. We continue to work and figure out a lot of these questions.

If it all ends at the end of the day today, we have failed. If we have more discussions and we can continue to learn and develop more ideas, then I think it will be a success. So, that's just a thought from me.

I want to, the last two days has given us a lot to think about. This has been very, very helpful. I have learned a lot and it has raised some very new ideas.

And rest assured, we've thought about this problem a lot, but there were a lot of new thoughts that came out in the last two days. And so that has been very helpful.

CTP and the regulated industry, we both have a lot of work to do to try to deal with some very, very tough problems. But I want to throw out another idea and that it's not just our problem, it's also the problem of all of us in the room here.

It's the problem of other...
government agencies. It's the problem of those folks in tobacco control. It's the problem of those folks in academia who have dealt with tobacco over the years.

To a large degree, we're in this together and we've got to continue to work with each other to try to figure out the best way to do this.

As was said just a few minutes ago, I know we will make a lot of mistakes along the way, but we will continue to learn and do that better as we go.

And the reason I say that we all have a responsibility, we need you to communicate with us. We have purposefully put up on the screen, over and over throughout this, the best ways you can communicate directly to us.

And there are a number of ways up here. I do want to point out clearly, they told me to make sure you understood, that if you type into your web browser,
regulations.gov, it won't work. You won't get where you need to go.

That's actually a hyperlink that was in the document that was sent out. So there is a way to get to that actual location. And that is on the CTP website, go to our web page and there is a way to tell you exactly how to get to that site.

So don't just type regulations.gov on your web browser, it's not going to get you where you want to go. So, just to clarify that.

So also, one other thing is I want to encourage everyone, we have some evaluation forms that are out, I'm not sure exactly where they are. I assume they're near the doors, that's where those things, or now, they may be in your packets. They're in your packets.

If you would fill those out, we would be very interested in getting your response to this. What worked, what didn't work, what other ideas you have, that would be
valuable to us.

   We're going to learn from this.

This is the first of what I hope will be not just the only one of these meetings, we hope to do this more and to continue to learn.

   I want to particularly thank all the panelists. You guys were great. You were very, very good. You provided some very interesting thoughts and ideas to us. Thank you very much for that.

   I also want to thank the audience who was very receptive, very quiet, listened very well. Thank you all for attending.

   I want to particularly thank Mr. Andrew Holtz, who I believe did an incredible job of bringing this out and I think he deserves a round of applause.

(Applause)

   DR. ASHLEY: I met Andrew for the first time on Wednesday, and it was a surprise in talking to him, how much he had already been involved in tobacco issues. I was afraid
we were going to have to give him hours and
hours of education to understand. And he
already understood a lot of the issues. And
he is a terrific questioner, and did a great
job of bringing out thoughts and ideas, and I
was very, very impressed with him.

And also, would like just to
recognize the folks on my staff and in the
other, the other folks right over here, the
contractors and the other folks from FDA, who
made this run so smoothly and I think they
deserve a round of applause also.

(Applause)

DR. ASHLEY: And just in final,
thank you all for being here. Again, this was
very, very useful for us and we hope it will
continue on, and we can continue to take
advantage of these kinds of meetings to learn
and to figure how to do our job better. Thank
you very much.

(Whereupon, the foregoing matter
went off the record at 3:05 p.m.)
<table>
<thead>
<tr>
<th>Page 339</th>
</tr>
</thead>
</table>
promoted 30:7,8
50:11 291:15
promotes 33:14
73:10
promoting 6:15
38:1 98:7 246:19
promotion 7:1
285:9
promotional 123:11
promotions 40:2
promulgated 47:17
proof 22:21
proper 290:3
properly 230:6
properties 35:15
proportion 143:20
206:9
proposal 82:6
proposed 116:19
117:16 188:17
proprietary 268:6
269:5
prospect 24:3
prostate 71:10
protect 27:14 35:7
35:19 74:13
287:17 296:5
313:3
protected 74:13
protecting 58:1
Protection 26:1
protocol 186:20
187:1 188:6,15
protocols 173:4
177:10 187:19
188:18 206:15
221:15 226:1
prove 253:11
provide 21:4 78:3
107:8 111:7
114:18 134:14
152:3 201:8 223:4
231:19 255:17
264:4,8 318:15
319:6
provided 105:10
150:21 180:15
324:8
provides 18:19
131:11 210:13
225:14,18,22
227:4 290:9
providing 113:12
115:2 211:5
227:13 262:7
proving 262:20
provision 24:6
102:9
provisions 102:22
118:14,18 182:22
proxies 168:8
proxy 145:13 146:6
165:9
psychiatry 135:11
236:10
Psychologist 209:18
psychology 2:10
105:3 106:19
120:7 135:11,15
209:19,21
public 1:6 2:13,15
4:4 5:21 24:21
26:13,14,17 27:14
27:21 29:6 30:5
33:6 35:7,19 36:9
47:8,9,21 50:9
51:20 55:17 57:7
58:14 77:13 78:4
78:9,17 79:3
82:22 83:8 87:11
90:14 94:3,4 95:6
98:6,9 99:7
102:14 103:1,5,9
113:4 120:20
128:21 129:15
134:21 146:1
148:13,22 149:2
149:12 159:4
168:15 171:13
172:15,21,22
174:9 178:16
179:16 200:10
207:21 209:11
211:8,9 215:16
216:4 226:14
246:11 266:16
282:10 283:8,20
285:9 286:8,18
288:2 290:1
292:22 295:6
296:3,5 302:3,4
305:15 313:11
publications 13:18
19:16 59:2
public's 211:15
313:3
publish 183:16
published 25:6
58:19 120:17
227:7 243:7
246:14
PubMed 58:21
puff 109:16
pulled 232:14
pulling 239:3
pulmonary 8:8
purchase 152:15
160:9,15,18
268:15 269:6,16
purchased 273:2,4
273:6,7,14
purchases 273:14
purchasing 162:14
pure 124:8
purely 197:2
purpose 85:20
145:16 225:9
237:13 258:9,12
purposefully 322:15
purposes 231:1
261:6
purposive 215:9
pursuing 113:6
push 77:3 144:6
213:6
put 28:1 32:2,8
90:11 108:10,18
109:2 127:18
137:3,20 149:10
164:10 175:17
198:17 202:14
204:16 214:11
244:13 250:5
255:18 259:6
266:17 275:21
282:1 293:6
296:22 300:17
302:19 304:19
305:8,13,14 307:8
322:15
puts 137:14 161:4
putting 136:18
191:16 197:16
206:2 278:6 284:4
307:5
P-R-O-C-E-E-D-...
4:1
p.m. 207:16,17
325:22
Q
qualifiers 202:10
qualifying 126:8,14
qualitative 131:11
132:14,17 134:15
150:19 151:16
152:2,6 174:12
175:4 203:15
quality 219:14
225:6 257:6
271:21 320:5
quantifiable 11:14
quantified 83:16
quantify 216:12
quantitative 9:15
64:3 131:8 132:20
134:15 139:15
152:7 174:13
quarter 15:5
quarterly 269:17
quarters 66:19
Quest 49:3 80:21
89:2
question 7:15 14:1
27:5 32:2 61:5
63:5 65:18 67:14
69:13 82:7 92:9
99:4 107:3,11
108:17 122:17
149:14 150:10
151:10,20 223:14
230:11 245:16
248:15 250:5,7
253:4 255:13,20
263:3 271:13,17
278:2 274:11
277:12,17 284:11
285:1 299:9,12
305:17 310:19
questionable 286:13
questioned 36:4
questioner 325:4
questionnaire 151:10,19
questions 4:21 5:2
27:3,5 72:19
104:4,7 119:22
144:16 176:12
181:11 206:12
208:8 215:11
230:6 234:16
248:4 249:4
251:6 258:9,21
259:22 279:12
281:12 321:2
quick 54:20 122:10
127:10 261:15
274:10
quickest 45:2
quickly 123:7
132:10 171:10
232:10 243:20
276:22 288:18
317:10
quiet 324:12
quit 15:5 29:14
47:4 48:11,12
51:17 59:4,18
62:17,18,20 63:3
66:14,15 67:1
73:17 76:3,6,12
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This is to certify that the foregoing transcript

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Before: Food and Drug Administration

Date: 08-26-11

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was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

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Court Reporter

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