Recent Advances In Tobacco Science

Volume 42

Population Health Standards for Tobacco Regulation

Symposium Proceedings
70th Meeting
TOBACCO SCIENCE RESEARCH CONFERENCE

September 18-21, 2016
Palm Beach Gardens, Florida USA
Symposium of the 70th Tobacco Science Research Conference

Population Health Standards for Tobacco Regulation

– Symposium Chair –
Chris Proctor

– Editors –
Ian Fearon
Kathy Humphries
Brian Nordskog
CONTENTS

Contributors ........................................................................................................ IV

Preface ................................................................................................................... V

Introduction to Symposium .............................................................................. 1
   Chris Proctor

POPULATION HEALTH STANDARDS FOR MODIFIED RISK
TOBACCO PRODUCTS .................................................................................. 3
   Conrad J. Choiniere

PREDICTING THE POPULATION HEALTH EFFECTS OF
CHANGING TOBACCO EXPOSURES: STATISTICAL MODELS
FOR REGULATORY COMPLIANCE ............................................................... 9
   Annette M. Bachand

DESIGN AND IMPLEMENTATION OF PRE- AND POST-
MARKETING SURVEILLANCE FOR TOBACCO PRODUCTS .......... 23
   Saul Shiffman

CONSUMER TESTING TO ADDRESS POPULATION HEALTH
STANDARDS FOR TOBACCO PRODUCTS .................................................. 43
   Geoffrey M. Curtin

Information for Ordering Previous Symposia ................................................. 55
Symposium of the
70th Tobacco Science Research Conference

Population Health Standards
for Tobacco Regulation

– CONTRIBUTORS –
Annette M. Bachand
Conrad J. Choiniere
Geoffrey M. Curtin
Karen K. Gerlach
Saul Shiffman
Sandra I. Sulsky
The Program Editorial Committee of the 70th Tobacco Science Research Conference is pleased to present the 42nd volume of Recent Advances in Tobacco Science publication. Each year the Program Editorial Committee of the Conference selects a theme that highlights a scientific or regulatory issue that is relevant, engaging, and thought-provoking for the tobacco community. The committee has chosen “Population Health Standards for Tobacco Regulation” for this year’s symposium theme. The symposium approaches the topic initially from an FDA perspective with a focus on submitting MRTPa’s. Statistical predictive models for possible consequences on population mortality and surveys for both pre-market assessments and post-market surveillance will be addressed. The design and use of consumer testing examining ‘comprehension and perceptions’, the ‘likelihood of use’ and the consumers’ understanding of a modified-exposure or a modified-risk message will round out this subject. Four distinguished authorities were invited to discuss research related to harm reduction and product risk. This publication contains the synopses of the symposium presentations and introductory remarks that include a brief biographical sketch of the symposium speakers. Members of the Program Editorial Committee, Ian Fearon, Kathy Humphries and I, wish to express our sincere appreciation to the speakers, Drs. Conrad Choiniere, Annette Bachand, Saul Shiffman, and Geoff Curtin and their colleagues for the significant time and effort spent preparing the publications and presentations, as well as Dr. Chris Proctor for acting as Symposium Chair. Information on ordering additional copies of this publication, as well as previous volumes, is included at the back of this book.

Brian Nordskog, Chair  
Program Editorial Committee 
70th Tobacco Science Research Conference
INTRODUCTION TO THE SYMPOSIUM

Chris Proctor

British American Tobacco (Investments) Limited
Southampton, United Kingdom

Basing tobacco regulation on a desire to protect the entire population, rather than just tobacco consumers, is not new. Restrictions on marketing and advertising, bans on characterising flavours and public place smoking bans all have, in part, roots in seeking to protect non-tobacco users and particularly vulnerable groups. What is new is the requirement for regulators to make a judgement prior to the marketing of a new tobacco product on whether that product will negatively impact population health. Measuring behaviour and perceptions post-market is reasonably easy as long as a new product gains sufficient popularity to allow study. Developing tools that accurately predict the future behaviour of the populations pre-market is challenging for both the industry and the regulator, and as such this symposium is both timely and important.

Both the Institute of Medicine’s (IoM) 2012 report on Scientific Standards for studies on Modified Risk Tobacco Products and the FDA’s 2012 draft guidance to industry on Modified Risk Tobacco Product applications (MRTPa) provide an outline of the types of studies that could be conducted and to what standard they are needed. The IoM tackled the difficult issue of the tobacco industry undertaking studies on vulnerable populations, and especially those under the legal age to use tobacco products, by suggesting several mechanisms for using independent third parties. While much of the IoM guidance is non-prescriptive, in some areas it is quite directive. For example, on the issue of risk communication it reports that the industry should use statements of absolute rather than relative risk, clearly state what type of risk and outcome is being addressed, under what conditions of use are the risks/benefits incurred, what comparison is being made, and what population incurs the risk. On the development of statistical models to integrate the data and predict population benefit or harm, the IoM report calls for transparency, validation and descriptions of uncertainties.

To begin the examination of this research topic, Dr Conrad Choiniere sets out what is likely to be required from the Food and Drug Administration’s (FDA) perspective. While considerations of population health are given to all new product pathways, modified risk tobacco product applications bring sharp attention in particular to the issues of abuse liability, risk perception, comprehension of risk and intentions to use. By providing insights to the questions that FDA are likely to ask of anyone submitting an MRTPa, and the types of scientific studies that could be responsive to such questions, he suggests the universe of research that is needed and ways to integrate the data for the regulator.

Dr Annette Bachand looks at the case of modified risk tobacco products and how statistical models may help predict the possible consequences on population mortality by considering both the intended beneficial effects and the potential for unintended harmful consequences. By building models based on existing population data it is possible to calibrate the tool before testing with two scenarios, one where only cigarettes are available and a counterfactual scenario which assumes the presence of an MRTP alongside the availability of cigarettes. Such models could be extremely valuable in determining tipping
points, *i.e.* the proportion of the population that must choose a less harmful exposure to overcome population level harm resulting from a subset of the population choosing a more harmful exposure, or vice versa. Dr Bachand explores the difficulty of gaining sufficient information on the population, such as historic exposures, and the impact of this on the likely accuracy of the predictions.

Dr Saul Shiffman focuses on the use of surveys both in pre-market assessments and in post-market surveillance schemes. He notes the importance of considering both the survey design and the population being studied. He also provides several examples of existing publically available surveys and other sources of information, such as Poison Control Centers or social media, which could be used to supplement the evaluation of a product’s use in the market post launch. He notes that there are some substantial practical issues in using surveys, particularly if the product only gains a small market share.

Dr Geoff Curtin provides examples of the design and use of consumer tests seeking to examine the areas of ‘comprehension and perceptions’ and the ‘likelihood of use’. In this he examines both the practical and conceptual challenges of collecting this data. While covering all of the FDA’s pathways to market, Dr Curtin brings focus to the additional challenged posed in a MRTP application, where there is a need to evaluate the consumer comprehension of a modified-exposure or a modified-risk message.

The area of population risk studies in the field of tobacco regulation is relatively new. To date, no modified risk tobacco product applications have been granted a marketing order, and the only application that has been reviewed, for a number of Swedish snus products submitted by Swedish Match, were granted a pre-market tobacco application marketing order where the review noted both methodological and data reporting concerns related to some of the population health related studies. Until some additional products have completed a pathway to market, there will be considerable uncertainty as to which studies will be acceptable to the regulator and what level of precaution the regulator is seeking to apply.

Perhaps statistical modelling can be of great assistance in analysing the sensitivity of the input data created in the series of studies needed to predict future behaviours on long term population morbidity and mortality. For example, if the solus use of an e-cigarette were to be 5% of the risk of the solus smoking of cigarettes, as has been suggested by the UK Royal College of Physicians, then, as Dr Bachand discusses, it should be possible, for example, to determine the proportion of non-tobacco users who initiate e-cigarette use needed to reverse the potential population health benefits of smokers switching to e-cigarettes. The magnitude of this tipping point could be examined, and thus the likelihood of a positive population health effect being changed to a negative one could be evaluated. Identifying such events would allow greater concentration on the tests used to evaluate these transitions.

Studies that predict population effects of new tobacco products pre-market and measure population effects post market are an important emerging scientific field that should lead eventually to consensus between the regulator and the regulated industry, with support from academia, on the preferred design and conduct of pivotal studies. This symposium provides a good beginning by identifying the current state of art, and what is needed to make rapid progress.

Chris Proctor
70th TSRC Symposium Chair
Abstract
The passage of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) in 2009 granted the U.S. Food and Drug Administration (FDA) regulatory authority over the manufacture, distribution and marketing of tobacco products. Before tobacco manufacturers may market new products, they must obtain authorization from FDA. The Tobacco Control Act describes multiple pathways for introducing new products on the market, including Substantial Equivalence and Premarket Review. In addition, a manufacturer may submit a modified risk tobacco product application if seeking to market a product to reduce the harm of tobacco-related disease. Tobacco manufacturers must submit scientific data and information so that FDA can evaluate whether the products meet the statutory standards allowing the marketing of these products.

This presentation will provide an overview of the population health standards related to each of the pathways and examples of the types of scientific information that could be used to demonstrate whether products meet those standards, with a primary focus on the role of the social and behavioral sciences for assessing impacts on the population as a whole and modified risk tobacco products. Because of the complexity of tobacco products and the population health standards against which modified risk tobacco products must be assessed, manufacturers provide FDA a broad range of scientific information to enable evaluation of products. A multi-faceted scientific review carefully considers the risks and benefits to the population as a whole including the health risk to the individual users of the products and the impacts on non-users, including the likely impact on initiation and cessation of tobacco use.

Background
In 2009, the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 387k) was amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31), granting the Food and Drug Administration the authority to regulate the manufacture, distribution and marketing of tobacco products. The Act granted FDA direct jurisdiction over cigarettes, roll-your-own tobacco, and smokeless tobacco products, but also gave FDA the authority, through rulemaking, to assert jurisdiction over other tobacco products. In May 2016, FDA acted on that authority, deeming jurisdiction over
any products that meet the statutory definition of a tobacco product, \textit{i.e.,} “any product made or derived from tobacco that is intended for human consumption” that is not a drug, device or combination product (as defined in the FD&C Act).

As part of its authority, FDA reviews tobacco product applications prior to authorizing products to be marketed. The standards used to assess tobacco products do not correspond with those FDA applies in the review of other products, such as medical products, which are assessed against standards of safety and efficacy. Rather, the standards correspond to an assessment of the impacts of tobacco products on the health of the population as a whole, often referred to as the population health standard. The population health standard is actually a set of standards established by the Act by which FDA is required to make regulatory decisions. In the case of the Substantial Equivalence (SE) pathway to market, the standard for FDA is to determine whether a new product has the same characteristics as a predicate product (a tobacco product marketed as of February 15, 2007) or whether any differences in the characteristics “raise different questions of public health.” For the Premarket Tobacco Product Application (PMTA) pathway, the standard requires FDA to determine whether “permitting such tobacco product to be marketed would be appropriate for the protection of the public health.”

In addition to new products, FDA may allow the marketing of modified risk tobacco products, \textit{i.e.,} tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. For the Modified Risk Tobacco Product Application (MRTPA) pathway, the standard requires FDA to determine that the product, as it is actually used by consumers, will “significantly reduce harm and the risk of tobacco-related disease to individual tobacco users” and “benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.” In a Special Rule included within the modified risk provisions, FDA may authorize certain products to make statements that the tobacco product or its smoke does not contain or is free of a substance; or, the tobacco product or its smoke contains a reduced level of a substance; or the tobacco product presents a reduced exposure to a substance in tobacco smoke. Here, the standard requires that allowing the product to market “would be appropriate to promote the public health.” However, the pathway is limited to cases where the scientific evidence on impacts to individual and population health is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies. In addition, the scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.
When considering questions of public health and the health of the population as a whole, FDA assesses not only the impacts on individual users of tobacco products but also impacts on those that do not currently use tobacco products, which may include never or former users. In the case of PMTA and MRTPA, the Act explicitly requires FDA to consider how the product (including the label, labeling and advertising) may affect the likelihood of cessation or initiation of tobacco products. Generally speaking, the population health standard (or the set of standards) requires FDA to consider the social and behavioral aspects of tobacco use. Thus, understanding how tobacco products, or the labeling and advertising of those products, affect the health of the population as whole entails a rigorous assessment of a wide range of scientific information about the product (chemical, engineering and microbiological sciences), about the user of that product (toxicological, pharmacological, and medical sciences), and the population (epidemiological, social and statistical sciences).

Modified Risk Tobacco Product Applications

The modified risk tobacco product provisions of the FD&C Act may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use. However, Congress, in its Findings to the Act, cited that “[u]nless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health…” To prevent any harm that may be caused from products sold or distributed as modified risk tobacco products that do not in fact reduce risk or harm to individuals and to the population, FDA must apply rigorous criteria for the review of scientific information to ensure that the products will benefit the health of the population as a whole.

FDA must assess whether an applicant, in its MRTPA, has demonstrated that the product will or is expected to benefit the health of individuals and the population as a whole. In order to make the demonstration, an MRTPA, generally speaking, will contain a wide range of scientific information. This information will likely touch upon the three broader aspects noted above (product, user, population) and address the health risks of the tobacco product; the effect the tobacco product and its marketing may have on tobacco use behavior among current tobacco users (including cessation); the effect the tobacco product and its marketing may have on tobacco use initiation among non-users (both never users and former users); the effect of the tobacco product’s marketing on consumer understanding and perceptions; and the effect the tobacco product and its marketing may have on the population as a whole. Thus, an application could contain some combination of product analyses (e.g., harmful constituents or design features), toxicological and pharmacological analyses, clinical or observational studies to assess health effects and abuse liability, as well observational or experimental studies to assess potential impacts on product use (e.g., experimentation, adoption, cessation or dual use).
Scientific Information to Address Social and Behavioral Considerations
When considering the impacts on the population as a whole, the measure of potential harm from a tobacco product entails an integration of information about the health risks to those that use the product with information on the extent to which the product is used in the population. Thus, in addition to information about the product (such as constituents) and health risks to the individual, the population health standard includes consideration of the social and behavioral aspects of tobacco use. For example, a clinical study may show that use of a tobacco product results in a significant reduction in harm and the risk of tobacco-related disease to the cigarette-smoking participants in the study that have switched from smoking to use of the tobacco product. However, in order to determine the product’s impact on the population as a whole, one would also consider a number of social and behavioral issues, such as (but not limited to) whether cigarette smokers in the population would adopt the tobacco product, whether those adopters would completely switch to the product or dual use with cigarette smoking, whether those that use the product actually use the product in a manner that reduces the risks as compared to cigarette smoking, whether use of the product delays cessation of tobacco use among those who may have otherwise quit tobacco, and whether current non-smokers and non-users of tobacco products might experiment with the product (and progress to established tobacco use).

Addressing these questions – and others related to assessing likely behavioral outcomes prior to a product going to market – may be addressed using information from a variety of types of studies: quantitative and/or qualitative, small-scale to large-scale, experimental and/or observational, as well as statistical modeling techniques. Given that the product in question may not already have been on the market, multiple threads of information (i.e., from multiple types of studies) may more adequately address these questions rather than information from a single study. Three types of categories of studies (and combinations) are commonly used by researchers to address the types of questions that may be asked about new tobacco products or modified risk tobacco products: surveys, consumer perception studies, and computational modeling of population effects.

Surveys
Nationally representative surveys might provide useful information about attitudes, beliefs and behaviors related to tobacco products which may provide insight on how consumers may respond to a new product when it goes on the market. For products already on the market, surveys can provide direct information. For new products not already on the market, surveys can provide indirect information that may be extrapolated to make inferences. The extent to which valid inferences can be made using the survey information will be related to the extent that the new product is similar to other products already on the market. However, indirect information from surveys may also provide some information about the types
and/or proportion of individuals that may be willing to try a new tobacco product or a product that is marketed as modified risk (regardless of the type or novelty of the product).

**Consumer Perception Studies**
Consumer perception studies can provide data regarding how consumers perceive the risks to health from using the product, and the likelihood of trying the product. Furthermore, these studies can provide data regarding consumer understanding of the product’s instructions for use and of the information concerning modified risk. Methods for consumer perception studies include both qualitative (e.g., focus groups) and quantitative (e.g., experimental studies) that often include assessments of consumer reactions after single or multiple exposures to products, labels and advertisements. In the context of modified risk, these studies may be useful to assess what messages are effective at conveying modified risk information to consumers, particularly when testing several variations of the proposed information on labels and/or in advertisements. In the case of the Special Rule within the modified risk provisions, these studies may provide insight as to whether claims about reductions in exposures to harmful constituents convey to consumers that the product has been demonstrated to reduce the risks of tobacco-related diseases.

**Computational Modeling**
Given the inherent difficulties in making premarket assessments of the effect that the introduction of a new or modified risk product would have on the population as a whole and the public health, researchers may opt to develop and apply innovative analytical methods to make preliminary estimates of the potential impacts of the new or modified risk product on tobacco use behaviors and the market for tobacco products. Methods for making similar estimates are commonly used in the fields of economics, statistics, decision sciences, and demography, and include secondary data analyses and computational modeling. Many models exist in the scientific literature to forecast the harm to public health from tobacco use. These models may provide some estimates of the effects on the population as a whole, by, in effect, integrating information regarding the potential effects of a new or modified risk product on health, tobacco use behavior (including cessation) and tobacco use initiation to provide an overall assessment of the potential effect that the product’s introduction to the market may have on overall tobacco-related morbidity and mortality.

As an illustration, consider a product that is estimated to pose one tenth of the risk of death from lung cancer as compared to smoking cigarettes. A model may quantify the potential changes in mortality to the various types of affected individuals in the U.S. population, for example by estimating the number of smokers that are likely to completely switch to the product and the subsequent reduction in the number of lives lost due to tobacco use, the number of smokers...
who may use the product in conjunction with other tobacco products and the subsequent effect on the number of lives lost due to tobacco use, the number of smokers who may have otherwise quit tobacco who instead use the modified risk product and the subsequent effect on the number of lives lost due to tobacco use, as well as the number of non-smokers that may initiate use of tobacco with the product and the subsequent increase in the number of lives lost to tobacco use.

**Conclusion**

The population health standards require FDA to consider impacts on the health of the population as a whole. Population health impacts result from the impacts the product has on the health of users of the product, the extent to which the product is used in the population and the patterns of use among those who use the product. Whether the net impact on the population is beneficial or harmful will largely depend on whether, how, and by whom, the new or modified risk products are used. Social and behavioral scientific information can provide information on whether, how, and by whom, and provide insight about the potential impacts of new and modified risk tobacco products prior to market. In particular, the information from social and behavioral studies can be integrated with the information about the product’s impacts on an individual to infer the potential benefits and harms of a new product on the population as a whole.
PREDICTING THE POPULATION HEALTH EFFECTS OF CHANGING TOBACCO EXPOSURES: STATISTICAL MODELS FOR REGULATORY COMPLIANCE

Annette M. Bachand and Sandra I. Sulsky
Ramboll Environ
Amherst, MA USA

Abstract
The Family Smoking Prevention and Tobacco Control Act of 2009 (the FSPTCA) mandated that FDA assume regulatory authority for tobacco products. A key provision of the FSPTCA states that FDA shall grant a modified risk tobacco product (MRTP) order only if an applicant has demonstrated that, among other conditions, the new tobacco product will result in reduced harm with no concomitant increase in risk to the population as a whole. This implies that both the intended, beneficial consequences and the potential for unintended, harmful consequences must be considered. Because the context for such evaluations involves predicting the potential effect of a new exposure, statistical models are necessary. By comparing counterfactual scenarios where cigarettes and the MRTP are available with a base case where cigarettes are used exclusively, statistical models estimate changes in population mortality which might result from projected changes in exposure patterns. Model results can be used to predict the magnitude, and thus likelihood, of changes in exposure patterns needed to produce population benefit or harm. To be responsive to regulatory requirements, models must be based on a scientifically valid conceptual framework. They must be flexible, allowing users to input and modify scenarios easily, and all required assumptions must be clearly documented. Models should be calibrated and results should be validated against existing population data. We examined the specific model requirements identifiable from the FSPTCA, and assessed each of several published models proposed to satisfy regulatory requirements. Most are not directly relevant to regulatory requirements or suffer from conceptual shortcomings. In particular, models that attempt to project the effects of introducing an MRTP to a cross-sectional, mixed age population require untenable assumptions and may produce biased results due to missing exposure histories and incomplete follow-up.

1. INTRODUCTION
   1.1 Background
Conceptually, the success or failure of a public health policy intended to reduce population harm can be determined by measuring changes in population mortality and morbidity. While reductions in these measures are expected and hoped for, unintended consequences that result in harmful exposure patterns also
can occur. It is the responsibility of policy makers to consider both the intended, beneficial consequences and the potential for unintended, harmful consequences of proposed policies, and to assess the likelihood and magnitude of both.

The relevance of these concepts to tobacco control stems from the regulatory landscape that emerged with passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) in 2009.[1] The FSPTCA assigned the responsibility of regulating the tobacco industry to the U.S. Food and Drug Administration (FDA). Section 911 (Modified Risk Tobacco Products (MRTP)) of the FSPTCA specifies that FDA shall issue an MRTP designation if an applicant has demonstrated, among other conditions, that a tobacco product will (1) significantly reduce the risk of tobacco-related disease to individual users, and (2) is likely to benefit the health of the population as a whole. While reducing a harmful exposure in individuals (e.g., due to switching from smoking to MRTP use) logically should lead to reduced population harm, increases in population harm might nonetheless occur if more people begin using tobacco and/or if fewer people stop using tobacco because of the availability of an MRTP. As a result, the FSPTCA states specifically that an applicant for an MRTP order must take into account the “likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application” as well as the “likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application”. The applicant is further required to enable the FDA “to review the accuracy of the determinations upon which the order was based”. [1]

1.2 Statistical models
Statistical models can be used to estimate changes in population morbidity and mortality which might result from projected changes in exposure patterns. In addition, models can predict the magnitude, and thus likelihood, of changes in exposure patterns needed to produce population benefit or harm. If such changes are due to regulatory action, then modeled results allow direct assessment of the health impacts of alternative policies, thus supporting the selection of one policy over another as well as providing information needed for regulatory compliance.[2]

To be useful in the regulatory context, models must fulfill a minimum set of requirements (Figure 1). These include a conceptual design that is directly relevant to the regulation; a model development strategy that follows sound scientific and statistical principles; demonstrated validity; transparency (the model should be subject to peer review and should be accessible to stakeholders); and easy accommodation of updates and expansions.
2. STATISTICAL MODELS IN THE REGULATORY CONTEXT

2.1 Conceptual design
Statistical models in the context of the FSPTCA must allow for the evaluation of the magnitude of the population shifts necessary to meaningfully increase or decrease harm. Requirements are laid out in the FDA Draft Guidance for Industry. [3] For tobacco products, intended, beneficial consequences of widespread availability of an MRTP include switching to MRTP use by some current cigarette smokers who otherwise would have continued to smoke, and initiation of tobacco use with the MRTP instead of cigarettes by some never tobacco users who would have initiated cigarette smoking. Unintended, harmful consequences include initiation of MRTP use by some never tobacco users who otherwise would have remained never tobacco users; transitioning to cigarette smoking after initiation of tobacco use with the MRTP by some who would have remained never tobacco users (i.e., gateway to smoking); and, switching to MRTP use by some current cigarette smokers who otherwise would have quit smoking.

Models should also allow for tipping point analyses. A tipping point is defined as the proportion of the population that must choose a less harmful exposure to overcome population level harm resulting from a subset of the population choosing a more harmful exposure, or vice versa. Such analyses are essential in the regulatory context because they allow for the examination of the magnitude, and thus likelihood, of consequences of increased availability of the proposed MRTP.

2.2 Development
Model population and time variables
The conceptual design elements described above can be incorporated most validly in a model that follows one birth cohort as it ages. The number of required
model input parameters is relatively small, input values can be tracked easily and, therefore, underlying assumptions are clearly defined. Sets of model runs can specify various potential tobacco use and mortality risk scenarios and the effect of any one input parameter can be assessed by systematically changing its value while holding all other parameters constant. Scenarios that account for multiple transitions to both harmful and beneficial exposures can be constructed to obtain an overall assessment of the potential effect of introducing the proposed MRTP to the population. Each cohort member’s entire exposure history is known and all deaths are accounted for. Model results can elucidate the magnitude of behavior changes needed to produce population benefit or harm, and combinations of scenarios can be defined to investigate tipping points.

While results from models based on a single birth cohort can provide insight into the likely effect of introducing an MRTP to an actual cross-sectional population, they do not provide predictions of changes in smoking prevalence or mortality in this population resulting from changes in tobacco exposure patterns. An alternative, conceptually appealing, but ultimately flawed approach, where a cross-sectional population of mixed ages and tobacco exposures is followed into the future, has been proposed by some authors.[4-6] Simulations start with a cross-section of an actual population stratified by age, gender and smoking status (current, former (by years since quitting) and never). The initial cross-sectional population is followed over time, necessitating two time variables, age and calendar year. Follow-up occurs until a pre-specified age or the end of the follow-up period has been reached. Some models are restricted to the initial cross-section, and some allow for new members to be added to the study population during follow-up through births. One model also allows changes to the study population through in- and out-migration.[5] Each of these models attempts to predict future mortality and/or smoking prevalence under exposure scenarios that include specified rates of initiation and cessation of cigarette smoking and use of a new MRTP.

While seemingly intuitive, the cross-sectional approach suffers from several shortcomings. First, neither the effect of MRTP initiation nor the effect of MRTP initiation followed by smoking (gateway effect) can be assessed validly. This is because the study population consists of a large number of birth cohorts, one for each year of current age represented in the initial cross-section, and one for each year during the follow-up interval when births are added. Births, migration, exposure, and mortality rates for a large number of birth cohorts cannot be predicted far into the future, so follow-up must necessarily be short (follow-up periods of 20-50 years have been suggested) [4-6]. As a result, tobacco-related mortality may not take place until after the end of follow-up for a sizeable proportion of the study population, due to the decades-long induction period for the most important tobacco-related diseases (lung cancer; heart disease; and non-malignant respiratory disease). This is specifically the case for younger members
of the initial cross-sectional population and for members of birth cohorts added during follow-up. The incomplete follow-up for mortality results in artificially low mortality risks among the younger subsets of the study population, i.e., those persons most likely to initiate tobacco use with an MRTP. In addition, for current smokers in the initial cross-sectional population or for those added through immigration, neither age at smoking initiation nor the number of years of smoking is known. As a result, mortality rates, which depend heavily on these factors, cannot be estimated validly. [7-11]

A second shortcoming of the cross-sectional approach is that neither the effect of switching from smoking to MRTP use nor the effect of smokers adding MRTP use (i.e., becoming dual users) can be assessed. This is because follow-up is too short for current smokers who add or switch to MRTP use later in the follow-up period to experience a change in risk, again due to the follow-up period being shorter than the induction period for smoking-related diseases. Also, for those who switch to the MRTP completely, follow-up may be shorter than the interval needed for risk to be reduced after quitting.

Third, the initial cross-sectional population only contains survivors. Therefore, current and former smokers in the initial cross-section who have a large amount of accumulated smoking exposure (i.e., many pack-years of smoking history) are less likely to be affected by tobacco-related mortality, susceptible members of the cohort having died prior to initiation of the simulation. Therefore, the effect of switching to, adding, or initiating MRTP use is artificially reduced in this subpopulation, and the mortality risks estimated on the basis of their experience is lower than risks experienced by subsequent cohorts.

Finally, the need to incorporate two time variables, age and calendar year, into the cross-sectional approach increases complexity compared with the single birth cohort approach. Specifically, model input values stratified by two time variables are more difficult to obtain, necessitating age and calendar year restrictions and estimated input values that are not substantiated by the literature.

Exposure transitions and transition probabilities
Any model developed to comply with the requirements of FSPTCA requires a comparison between a counterfactual scenario, in which exposure to cigarettes and/or the proposed MRTP may occur, and a base case, in which cigarettes are the only form of tobacco available. The model should, at a minimum, allow for the most commonly observed exposure transitions including initiation and cessation of either product, relapse from quitting, subsequent cessation of either product, switching between products, and dual use. As population members are followed over time, survivors should be distributed into age and exposure categories using age category-specific exposure transition probabilities. Model users should be
able to specify the probability of transitioning from one exposure state to another based on available data or based on a particular question of interest, and these parameters should be easily modifiable to evaluate different scenarios and to carry out sensitivity analyses.

**Risk**
The statistical model must estimate the risk to the population that results from different exposure scenarios. Estimates for risk should be based on the available literature and should account for key predictors of the outcome measure selected. Key predictors of smoking-related mortality include age, duration of smoking and time since smoking cessation; amount of smoking also could be incorporated. Estimation of mortality risks is hampered by the paucity of available data, stratified by these predictors, for representative populations. While desirable, estimating smoking-related morbidity risk is more problematic than estimating mortality risk, largely because there is no standard definition of morbidity and it is not measured or tracked effectively.

For users of the proposed MRTP, which is by definition, a new product, risks are unknown and cannot be directly estimated. Instead, an adjustment factor such as an excess relative risk (ERR) for individuals with current (former) exposure to the proposed MRTP versus current (former) exposure to cigarette smoking could be used to reduce the risks estimated for current and former cigarette smokers. Alternatively, the model could use absolute risk estimates for the MRTP compared with non-users of tobacco.

**Model output**
To be responsive to the FSPTCA, the output of any model should allow for comparisons between the base case and counterfactual exposure scenarios at the end of a specified period of follow up. The comparisons could be based on numbers or rates of deaths or survival. To allow for tipping point analyses, deaths or survivors in the counterfactual scenario should be further classified by their exposure in the base case. For example, smokers who switched to MRTP use in the counterfactual scenario should be divided into those who continued to smoke and those who quit smoking in the base case. Quality of life adjusted life expectancy (QALE) may be used to approximate population morbidity. It can be estimated by multiplying life expectancy (LE), calculated according to actuarial principles, by a factor that accounts for disability, illness, or both.[12-16] The choice of output measures (differences in numbers of deaths or survivors, LE or QALE) depends on the question being addressed by a given analysis. Specifically, the difference in the number of deaths or survivors under two exposure scenarios provides a direct estimate of the effect of use of a new MRTP on population mortality. LE estimates can be used to plan for the delivery of health care, while QALE estimates provide a measure that approximates morbidity and is used by economists to choose
between medical interventions competing for the same resources.\cite{12, 13, 16, 17} Some authors also have suggested the estimation of smoking-attributable deaths.\cite{4, 5} However, attributable risk calculations do not account for competing causes of death and can thus add to more than 100\%, i.e. attributable risks for all risk factors for a specific cause of death, when combined, can explain more than the number of deaths observed. Therefore, calculating smoking-attributable deaths is of limited utility and estimates must be interpreted cautiously.

Variability

Model users should have the choice to enter input values such as transition probabilities and ERRs as fixed (most appropriate for values defining a specific question of interest) or with some degree of uncertainty (most appropriate for values based on estimates from the literature). Variability in the output measures should be estimated, for example, by using Markov Chain Monte Carlo (MCMC) techniques. Sensitivity analyses, where the model user generates results for a range of input values, can be informative, but do not replace variability estimates.

2.3 Validation and calibration

The sorting of population members into age and exposure states should be validated prior to implementing the full simulation. To calibrate the model, appropriate input data should be used to define a base case and, if possible, a counterfactual scenario whose model results can be compared to data from an actual population. Close correspondence between the modeled results and observations from the population indicate the model is well calibrated, and predictions based on the scenarios being tested may be considered valid.

2.4 Transparency and access

Critical review

Methods used to develop the model, all model assumptions and all input data should be clearly documented and made available, along with example results, for peer review. This can occur in the context of journal publications and/or presentations at scientific meetings. In addition, an effort should be made to allow for pre- and post-publication peer review. Ideally, development of the model and examination of its assumptions and performance will have occurred with stakeholder input, including input from the regulatory agency and the regulated industry. To facilitate this, the set up and operation of the model must be user-friendly, allowing users with no in-depth understanding of the programming language used for model development to recreate existing examples and to test new examples.

2.5 Updates and expansions

The model should be flexible enough to allow for the easy incorporation of new study questions or data. For example, the base case may require modification over
time, to represent changes in actual exposure patterns such as smoking initiation and cessation rates. Also, as the range of possible exposures changes, the model should be easily expandable, e.g., to compare a base case with two products to a counterfactual scenario with three or more products.

3. AVAILABLE MODELS FOR REGULATORY COMPLIANCE

3.1 Overview

To our knowledge, only five published dynamic population models have been specifically designed to estimate the effects of introducing an MRTP to a population. These models can be most easily distinguished by their study populations and time variables. The Dynamic Population Modeler, DPM(+) [18] and the model described by Levy et al. (2016)[19] were each designed to address the needs identified in the FSPTCA. Both are based on a single birth cohort which is followed as it ages. Weitkunat et al. 2015 [4], Vugrin et al. 2015 [5], and Poland et al. 2016 [6] have proposed models where simulations start with a cross-section of an actual population which is followed over time based on two time variables, age and calendar year. All five models allow modeling of a range of probabilities for each transition of interest to determine the potential magnitude and likelihood of a population benefit or harm to follow from introduction of an MRTP to a population.

Two other published models were designed to estimate the effects of introducing a new product to a population of never, current and former smokers, but the range of questions they can address is limited because they hold smoking initiation and cessation rates constant and do not allow transition probabilities to depend on age. Specifically, the model proposed by Apelberg et al.[20] allows for very few transitions, assumes that transition probabilities do not depend on age and that mortality risk depends only on current tobacco exposure status and no other exposure metric. The model published by Mejia et al.[21] also assumes that risk depends only on current tobacco exposure status and uses a very limited number of exposure states and transitions (e.g., quitters of tobacco cannot revert to tobacco use). In addition, the model uses the same initiation, cessation and transition rates for the entire hypothetical population, regardless of age and quantifies the risk of tobacco-related health effects by a health index that is assumed to be the same regardless of duration of tobacco use or cessation. The health index itself does not seem to be based on empirical data. A detailed critique of this model is published elsewhere.[22]

While other dynamic models focusing on risks associated with use of tobacco products have been described in the literature, most were developed to estimate changes in population-level risk due to changes in proportions of never, current

1Published models that have been proposed to support analyses relevant to the FSPTCA.
and former smokers resulting from increasing smoking cessation rates and/or decreasing smoking initiation rates; they do not consider the effect of introducing a new product to a population.[23-28]

All models must be built on simplifying assumptions. The five models discussed here share the following: (1) they compare the effects of using only two types of tobacco products; (2) only the direct effects of exposure to higher- and lower-risk tobacco products are considered; hence, the analyses do not account for changes to second-hand smoke exposures, for example, that are due to changes in the proportions of cigarette smokers in the population; and, (3) the models require the analyst to specify relevant input data.

### 3.2 Models based on a single birth cohort

To our knowledge, two existing models are based on the single birth cohort approach. As described elsewhere [18], the DPM(+1) is a comprehensive and flexible dynamic model that estimates all-cause mortality for a hypothetical birth cohort which is followed as it ages. All model input is user-specified. In the base case, members of the cohort may be exposed to a high risk product (i.e., cigarettes) as they age. The counterfactual scenario includes exposure to both the high risk product and a lower risk product (i.e., an MRTP). The model sorts the study population into age and exposure categories, and applies mortality rates specific to age, duration of exposure and duration of exposure cessation to each category. The model tracks individual exposure histories, and estimates, at the end of each modeled age category, the number of survivors in the two exposure scenarios (base case and counterfactual), and the difference between them. MCMC techniques are used to estimate the variability of the results.

The main strengths of the DPM(+1) are its flexibility, its ability to account for uncertainty in the model input and output, its comprehensiveness, and its demonstrated validity. All model input values can be changed by the model user, and the level of uncertainty in the input values can be specified and is accounted for by posterior intervals around the estimated differences in the numbers of survivors. There are no restrictions on age, time of initiation, or time of cessation of exposure. The DPM(+1) can be used to explore the potential magnitude and likelihood of population benefit or harm and to estimate tipping points. In addition, results from the DPM(+1) can provide insight into the effect of introducing an MRTP to a cross-sectional population if population members of different ages are recognized as members of different birth cohorts. However, it cannot directly provide absolute predictions of differences in survival in a cross-sectional population resulting from changes in tobacco exposure patterns.

The DPM(+1) is executed in the R language [29] both as a desk-top version and as the back end to an internet-accessible platform with a user-friendly interface.
that simplifies the recreation of existing analyses and testing of new scenarios. Post-market data can be easily incorporated. Expansions that are under way or have been completed include modeling exposure histories with more than two products and modeling the removal of an exposure from the market.

A model described recently by Levy et al. (2016) [19] follows a birth cohort of 15-year olds in 2012 (the 1997 birth cohort) as they age. Follow-up ends in 2083, *i.e.* at age 85. In the base case, only cigarettes are available. In the counterfactual scenario, different rates of trial and established use of a vaporized nicotine product (VNP), either alone or in combination with cigarettes, occur. Model output includes the proportion of the cohort in each exposure category at various ages, smoking-attributable deaths and life-years lost and gained; rates are provided in the supplementary materials published with the article, but details on the calculations are not provided. The authors completed sensitivity analyses by altering the estimated excess risks and rates of VNP trial and use. However, the model does not account for variability of the model input and variability of the results is not estimated.

### 3.3 Models based on a cross-section of the population

Three published models are based on a cross-section of an actual population (Weitkunat et al., Vugrin et al., Poland et al.)[4-6]. These models compare mortality between a counterfactual scenario where an MRTP is introduced during the follow-up period and a base case where only cigarettes are available. The models sort the study population into calendar year, age and exposure categories and track individual exposures during follow-up; for smokers in the initial cross-sectional population, age at onset of smoking and years smoked are unknown. The Weitkunat et al. model is restricted to the initial cross-section and deaths do not occur until the end of follow-up. Poland et al. and Vugrin et al. allow changes to the study population throughout follow-up through births and deaths. Vugrin et al. also take migration into account.

The models estimate total deaths in the base case and the counterfactual scenario. In addition, two of the models (Vugrin et al., Weitkunat et al.)[4,5] estimate smoking-attributable deaths in the base case and the reduction in smoking-attributable deaths in the counterfactual scenario and one model (Poland et al.) [6] estimates the reduction in total deaths. None of the models account for uncertainty in the model input values or provide variability estimates for the model outcome measures. Underlying assumptions are easily assessed for the Weitkunat et al. model and the Poland et al. model but not for the considerably more complex Vugrin et al. model.

In any modeling analysis, model results are highly dependent on the input data selected by the analyst, and should be substantiated to the extent possible. Two of
the three models based on an initial cross-section of a population require a large number of unobservable estimates of birth and death rates, and in one case rates of in- and out-migration. All three models require age- and gender-specific smoking initiation and cessation rates, corresponding to each year of follow-up into the future as specified by the analysis.

Weitkunat et al. and Poland et al. suggest several potential expansions of their model to take post-market data into account and the models appear simple and flexible enough to allow for the suggested adaptations. The model proposed by Vugrin et al. is very complex and requires large amounts of input data, making expansions difficult. Published validation and calibration exercises for all three models are incomplete and/or show results that do not lend credence to the approach.

Each of the three models has specific strengths and limitations. Their utility in the regulatory context is very limited, however, due to the inherent shortcomings of the cross-sectional approach that affect the validity and utility of the resulting predictions. Specifically, the models are limited by short follow-up periods. Given the decades-long induction periods for tobacco related causes of death, it is very unlikely that the introduction of an MRTP to a population will have a sizeable impact within a short follow-up period, especially if one considers that initiation of or switching to the new product is likely to occur throughout the follow-up period and not just in the beginning. Further, because estimates for the cross-sectional population are affected by survivor bias, results are not generalizable.

4. CONCLUSIONS
The regulatory landscape that emerged with passage of the FSPTCA resulted in the need for policy makers to determine if the introduction of an MRTP to the US population is likely to benefit the population as a whole. While reducing a harmful exposure in individuals (i.e., due to product switching) logically should lead to reduced population harm, increases in population harm might nonetheless occur if more people begin using tobacco and/or if fewer people quit using tobacco because of the availability of an MRTP. Both the intended, beneficial consequences and the potential for unintended, harmful consequences of proposed policies must be considered, and the likelihood and magnitude of both must be assessed. Five dynamic population models have been developed to assist with this effort but three of the five models are based on an approach whose shortcomings affect the validity and utility of the model predictions.

Defining the magnitude of change from the baseline number of survivors that is both likely to occur and large enough to impact population health is a decision that should be undertaken collaboratively with all the relevant stakeholders, preferably a priori. Care must be taken in defining meaningful differences between
the counterfactual scenario and the base case, and the rationale for these decisions should be documented.

Nevertheless, models are necessary to meet the requirements of FSPTCA pertinent to predicting the likely effect of introducing an MRTP to a market. If based on a solid and defensible conceptual framework, developed according to rigorous scientific principles, and if employing reasonable assumptions and justifiable input values, models will provide valuable information to policy makers choosing between different courses of action.

References
22. Bachand, A.M. and S. Sulsky, Critique of “Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA” by Mejia AB, Ling PM, Glantz SA. Tobacco Control Online, 2011.


DESIGN AND IMPLEMENTATION OF PRE- AND POST-MARKETING SURVEILLANCE FOR TOBACCO PRODUCTS

Saul Shiffman
Pinney Associates
Pittsburgh, PA USA

Abstract
Under the Family Smoking Prevention and Tobacco Control Act, the Food and Drug Administration may require pre- and/or post-market surveillance of tobacco products to assess the expected or actual product impact on population health. Although surveys are an important tool for surveillance, with both public-use Federal surveys and special-purpose surveys playing a role, considerable practical challenges arise when attempting to characterize use of products with a small market share, and significant conceptual challenges arise in attempting to link any one product to potential effects on the population as a whole, especially in a dynamic tobacco/nicotine marketplace. In addition to surveys, surveillance may require retrieval and analysis of data from other sources, such as calls to Poison Control Centers and emergency department visits. The development and implementation of tobacco product surveillance, including steps to address the practical and conceptual challenges, are discussed.

Introduction
With the passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) (2009), the Food and Drug Administration (FDA) was given the authority to regulate tobacco products in the interests of population health (U.S. Department of Health and Human Services, 2016). Surveillance of tobacco product use is an important part of fulfilling that mandate. As the FDA has issued guidances, held workshops and seminars, and responded to industry queries and applications, the expectations for surveillance are becoming more defined. The FDA has issued draft guidances on Premarket Tobacco Product Applications (PMTAs) (U.S. Department of Health and Human Services, 2016) and on Modified Risk Tobacco Product Applications (MRTPAs) (U.S. Department of Health and Human Services, 2012), both of which discuss the information the Agency recommends be submitted in support of such applications. Further, the Agency has made public its response to the PMTA approved for Swedish Match’s snus products. This approval included specific post-market surveillance requirements from the FDA (U.S. Department of Health and Human Services, 2015), and these documents can help regulated companies understand what the FDA is looking for and what a company might need to put in place to address the FDA’s concerns. This paper
reviews what is likely to be expected from tobacco surveillance programs, with a focus on the behavioral and health outcomes of interest to the FDA.

**Targets of Surveillance**

The mandate of the FDA's Center for Tobacco Products (CTP) is detailed in the FSPTCA law that created the Center (Family Smoking Prevention and Tobacco Control Act, 2009). CTP's task is to protect the public health from harm due to tobacco products. The Act specifically requires that when considering an application for pre-market authorization, for a reduced-exposure claim, or for a modified-risk claim, the CTP must consider the effects of the product not only on its users, but on the population as a whole. Establishing the direct effects of the tobacco product that is the subject of an application (hereafter referred to throughout as the “index product”) on its users is largely a matter of toxicology. But establishing the effects of the index product on the population as a whole also requires behavioral epidemiology to understand how the product is being used and by whom. One key outcome is whether the index product attracts new users to tobacco use or reduces quitting among current tobacco users. This concern is exemplified by a hypothetical reduced-risk product supported by toxicological and epidemiological data that establish a 20% reduction in risk for smokers who switch to the new product. If such a product increased the prevalence of use by 50%, it would result in net harm to population health. Thus, understanding the behavior of the population becomes critical.

Besides establishing who is using the index product, behavioral data are also important to understand how the product is being used. To link the toxicological data on the index product to actual risk incurred by its real-world users, the CTP needs to understand how users are using the product and how much of it they are using. Thus, behavioral data are important to interpretation of the toxicological data in a population context. Further, the release of a new index product into the market may yield new information about its safety, based on real-world users’ experience of adverse effects.

Accordingly, the MRTPA Draft Guidance (U.S. Department of Health and Human Services, 2012) recommends that the outcomes evaluated in postmarket surveillance and studies include the effect of the tobacco product on consumer perceptions (e.g., perceived risks to health due to use of the product), behavior (e.g., use of the product by those who were previously tobacco users and non-users), and health (e.g., the effect of the product on tobacco-related morbidity and mortality).

**Surveys for Surveillance**

Surveys are a primary instrument for collecting data about product users and usage patterns, and data to inform a product’s likely population impact. To collect
data across tobacco users and non-users, sponsors will need to survey samples of consumers, gathering self-reports on product usage, as well as beliefs, perceptions, and intentions relevant to use.

**Populations to be Studied**
Understanding who is adopting a product, and how they are using it is key to understanding the product’s likely impact on population health.

As noted in another paper by Curtin in this volume and discussed above, a product’s effects on population health do not depend just on its toxicology and its effects on the individual user’s risk, but also on who comes to use the product. This is clearest in the case of a modified risk tobacco product (MRTP) that has established that it materially reduces risk relative to cigarette smoking, but that still carries some level of risk. Switching to such a product would clearly benefit cigarette smokers. Conversely, adoption by a teenager who otherwise would not have used tobacco increases that user’s risk. At the population level, then, the net benefit/harm will be a function of adoption by target groups who stand to benefit and off-target groups who stand to be harmed. Accordingly, to understand the product’s population effect in the marketplace, one must track who is using it. Specifically, several key groups must be tracked, and these groups are defined by two features: (1) their tobacco use prior to adopting (or not adopting) the index product, and (2) their expected trajectory of tobacco use if the index product were not available. The first is history that can easily be ascertained in self-report data; the second is a hypothetical that can, at best, be imperfectly and indirectly projected from data.

1) Cigarette smokers. Cigarette smokers clearly stand to gain the most benefit, since they are “trading down” their risk from smoking to the MRTP. However, a smoker who otherwise would have quit tobacco use completely, thus eliminating all continuing tobacco-related harm (but for the long tail of risk after smoking cessation), would be harmed by shifting to the MRTP instead. Accordingly, the population of cigarette smokers breaks out into two hypothetical sub-populations:
   a) Cigarette smokers who would not otherwise have quit, and are thus benefitted.
   b) Cigarette smokers who would otherwise have quit, and are thus harmed.

2) Former cigarette smokers. There is a concern that individuals who have already quit smoking and quit all tobacco use might find an MRTP appealing, because it could change their risk/reward calculus for smoking. Whether adopting the MRTP benefits or harms former cigarette smokers depend on whether they would otherwise have relapsed to smoking, again resulting in two hypothetical populations:
a) Former smokers who would not otherwise have relapsed, and are thus harmed.
b) Former smokers who would otherwise have relapsed, and are thus benefitted.

3) Non-tobacco users. Just as with former smokers, the lower risk of the MRTP might make it appealing to individuals, including teens, who are not already using tobacco. Adoption by such individuals would be expected to increase harm, unless they were likely to have taken up cigarette smoking in any case, in which case being diverted to the lower-risk MRTP is beneficial, again yielding two populations:
   a) Never-tobacco users who would not otherwise have smoked, and are thus harmed.
   b) Never-tobacco users who would otherwise have smoked, and are thus benefitted.

In the post-marketing setting, where the index product has been available in the market, users of the index product would be identified. (In the pre-market setting, respondents can be asked about their interest in the index product; see Curtin, this volume). It will be clear that ascertaining survey respondents’ history of tobacco use and current use can be relatively straightforward, allowing them to be classified as smokers, former smokers, or never-tobacco-users. Projecting what they would have done, if they hadn’t in fact started using the index product, is much more difficult and, even at best, much less precise. The most logical approach would be to measure “risk factors” known to predict smoking or continued smoking, and assess adoption of the index product in groups with low and high risk. For example, among people who have stopped smoking, the risk of relapse to smoking declines steeply over time (Gilpin et al., 1997; Garcia-Rodriguez et al., 2013); thus, those who have been abstinent only briefly (e.g., up to 6 months) have a very high likelihood of relapsing to smoking; those who had been abstinent a long time have a much lower likelihood of relapse. Among teens, certain indicators of rebellion and risk-taking characterize those who are likely to smoke (Burt et al., 2000; Tyc et al., 2004), and may allow segregation of a sample into those who were likely to take up smoking and those who were not. However, these indicators are very, very far from perfect. They may nevertheless help hone the modeling of how the observed patterns of product use may eventually affect population health.

As discussed below, longitudinal studies have significant advantages for assessing the relationship between antecedent tobacco status and intentions and subsequent adoption of the index product. Tobacco use status and intentions or risk factors predicting subsequent tobacco use can be assessed at Time 1 related to subsequent adoption of the index product at Time 2.
Because the interest in the behavioral effects of product use is in the transitions among different categories of tobacco use, it is important to also capture the current behavior of individuals who previously used the index product. There is a concern that use of a reduced risk product could lead to use of higher-risk behavior such as cigarette smoking. This concern has particularly been expressed with regard to “gateway” effects (Barrington-Trimis et al., 2016; Haddock et al., 2001; Leventhal et al., 2015; Primack et al., 2015), whereby tobacco-naïve individuals who adopt a low-risk product, such as electronic cigarettes (or e-cigarettes), are hypothesized to thereby be caused to progress to cigarette smoking. Whether such effects in fact occur, and how frequently, is quite controversial (Bell et al., 2014; Kozlowski et al., 2003; Lee, 2015; Brown, 2016), but the concern is prominent in the tobacco control community. Cross-sectional surveys of current users of the index product would not be informative regarding gateway effects, as individuals who have gone through the gateway would now be smokers. Surveying former users of the index product and ascertaining how many of them are now smokers and how many are non-tobacco-users, may be regarded as informative. However, making causal inferences from such data is deeply problematic, because the very same individuals who are predisposed to smoke cigarettes (e.g., risk-seeking, rebellious individuals) are likely also predisposed to use e-cigarettes. Hence, observing an association by no means implies causation.

**Longitudinal surveys**

Longitudinal data that allows one to observe the transition from use of the index product to smoking (or abstinence), and to assess subject characteristics before the transition, or even before any tobacco product is used, can help with inferences about determinants of transitions in tobacco use, but inferences about counterfactuals (e.g., would this person have gone on to smoke anyway?) will remain problematic. The problem is that we have not identified many of the characteristics that predispose individuals to tobacco use, much less developed robust measures of these characteristics, making the threat of confounding intractable. Nevertheless, it will be important for surveillance to ascertain how often users of the index product progress to cigarette smoking (or, more generally, to a higher-risk tobacco product).

Because there is so much interest in transitions in tobacco use over time, a longitudinal design, in which a cohort of individuals is followed over time, seems a natural fit. (The Population Assessment of Tobacco Use and Health [PATH] study [Borek, 2016] uses such a design.) Longitudinal designs have significant advantages for tobacco product surveillance. They allow one to assess an individual's behavior and intentions prior to a change in tobacco use. For example, by assessing smokers' plans to quit at Time 1, and adoption of a MRTP at Time 2, one can assess whether smokers who were planning to quit were more or less likely to adopt the MRTP, which is relevant to evaluating the likely impact of that product on population
health. Information such as this is difficult to recover retrospectively in a cross-sectional survey, because respondents cannot reliably report what their state of mind was some time in the distant past, especially having changed their behavior in the interim.

Longitudinal surveys also have disadvantages. They may entail more severe self-selection bias at enrollment, since fewer people may be willing to sign on to a longer-term commitment. Selective drop-out from the cohort over time can significantly bias longitudinal inferences. Importantly, participation in the survey itself can bias subsequent behavior and subsequent responses, even just by forcing participants to contemplate their tobacco use behavior in detail, to consider health effects of tobacco, and to become aware of the range of tobacco products from which they might choose. The ideal surveillance program would include both longitudinal and cross-sectional components.

Survey Content
The nature of the data to be collected in surveillance should be directly determined by the objectives and by the concerns that the surveillance is designed to address. However, there are basic pieces of information that will almost always be relevant. Sponsors and the CTP will want to know who is using the index product and how they are using it. Surveillance should not focus solely on the index product – co-use of other tobacco products will also be highly relevant. As discussed, it will almost always be important to understand not only current tobacco use, but the history of use, and transitions between different categories of use (including abstinence).

The frequency and intensity of product use will almost always be relevant to evaluating the impact on population health. This will often be adequately captured by appropriately designed self-report measures, asking, for example, how many days per month and how many times per day the product is used. Some behaviors may be less suited to self-report. For example, puffing topography can be important in determining exposure, but is not amenable to assessment by self-report. If such issues are important for a particular product, it may be necessary to assess usage behavior in more detail using objective measures (or, possibly, biomarkers), either in the field or in the laboratory. This is particularly important to link the behavior reported in-market with the pre-market testing, which will have tested the product under particular expected patterns of use; post-market data can be used to confirm whether those usage patterns in fact hold, and thus whether the toxicological findings obtained in controlled circumstances hold in the population. There is considerable benefit to performing these more intensive studies with individuals strategically sampled from larger survey samples. It can be used to deliberately sample individuals based on their survey responses, to
represent in the smaller intensive studies the range of individuals and behaviors seen in the larger survey samples.

Because a common concern about reduced-risk products is that they may divert people from quitting tobacco altogether (the transition associated with the most risk-reduction), interest in and movement towards quitting, as well as recent history of quit attempts, should be included. There are well-established approaches to assessing these topics. Measures of addiction are also likely to be important foci for assessment. There are a variety of competing measures of dependence (Heatherton et al., 1991; Piper et al., 2004; Shiffman et al., 2004), almost all developed and validated in the context of cigarette smoking. Most recently, PATH has developed a measure that is claimed to work across different tobacco products, and to yield scores that can be compared across tobacco products (Strong et al., 2016), which has obvious advantages.

Consumers’ beliefs about the index product, such as their perceptions of its risks to health, may be an important influence on adoption of the product by various segments of the population. Accordingly, it may be important to assess such perceptions, as well stated intentions to use the index products, as a proxy for future behavior. As discussed in another paper by Curtin in this volume, pre-market consumer comprehension and perception studies need to be completed and submitted in support of MRTPAs, prior to marketing with MRTP claims. Those pre-market studies assess the impact of the proposed consumer communications in an artificial setting, typically by exposing consumers to the proposed communications, and assessing their understanding and beliefs. As noted in the paper by Curtin, the information thus obtained is limited by the artificial setting and the limited and forced exposure to messaging. Those studies, in effect, evaluate what the messages can communicate, and what consumers can take away from message exposure. In the post-market environment, the question shifts to what consumers actually understand and believe, when the product is in-market, and when they may have had multiple exposures to the product messaging, as well as exposure to other messages (e.g., via the media and internet). For example, there is concern that a product that reduces risk (but does not completely eliminate it) may come to be perceived as completely safe and just as safe as quitting tobacco and nicotine use altogether. Such beliefs would likely be seen as precursors to and drivers of behaviors that could undermine the product’s benefit to population health (e.g., adoption by non-tobacco-users or smokers using the product instead of quitting). Accordingly, risk perceptions may be relevant targets for surveillance.

Selecting or Developing Survey Items
How one asks a question influences the answers. Accordingly, careful attention to item wording is important. Wording should be clear and free from biasing language. The number and order of response options can also influence
responding; randomly rotating response options when they are not ordered is helpful in avoiding order bias. New survey questions should generally be pre-tested in two ways. First, small-scale qualitative testing (Beatty & Willis, 2007; Willis, 2005) can be used to ensure that respondents understand the question and interpret it as intended. Second, small quantitative pre-tests can give a preview of response distributions and can help detect problems.

There is considerable value in using items adopted from existing published surveys, especially well-established federal surveys. This ensures some degree of item testing and validation, and facilitates comparison across surveys and populations. However, existing survey items were often designed with different goals in mind, so adherence to precedent should not squelch development of new items where they are needed. Notably, as new tobacco products emerge, they will require new questions for which there will be no existing standards. For example, currently, there is no standard or validated method for assessing the amount of e-cigarette use (Amato et al., 2016).

Development of multi-item scales to assess complex constructs, such as tobacco dependence, is a far more complex and demanding undertaking, and detailed coverage is far beyond the scope of this paper. Suffice it to say that it is a multi-step process usually requiring research to be done prior to fielding the survey in which such scales are used. Existing validated scales should be used where possible.

Sampling
A key issue in survey research is how the sample is obtained (see Kalton, 1983). The ideal is a representative sample drawn randomly to represent the American population. This platonic ideal is simply not achievable. Even if one could reach and invite a truly random sample to complete the survey, completion of the survey is voluntary, and those who agree to do so may be different than those who decline (“non-response bias”). Further, even finding a truly random sample is difficult.

Random-Digit Dialing
Random-digit dialing, which involves dialing phone numbers at random (or through some more complex but randomized scheme) used to be the gold standard in survey sampling. However, with the advent of mobile phones, increasing numbers of the U.S. population, especially younger members, do not have fixed phone lines. Even on land-lines, more and more people use caller-ID to screen calls and will not answer a call from an unknown number. Accordingly, random-digit dialing has fallen off its gold-standard pedestal.

In any case, telephone interviews have significant limitations. For example, respondents must listen to questions read verbally, which is time-consuming and mentally taxing for the respondent. Long or complex response alternatives
are difficult to communicate. Visual stimuli (e.g., product pictures) and visual response options (e.g., visual analog scales) cannot be used. As a result, telephone surveys need to be limited in length and complexity. Increasingly, surveys are fielded online, with stimuli and questions presented on-screen, and responses entered by clicking or through keyboard actions. Online survey administration also allows complex skip patterns, random rotation of response options, and a host of other “smart” survey administration options.

Online Panels
Online survey administration is often linked to online recruitment of the sample, though it need not be. Probably the most common current method of recruiting for surveys is the use of online survey panels. These are composed of individuals – often millions of individuals – who have agreed to participate in surveys in return for some sort of compensation, usually points redeemable for goods. How individuals are recruited into the panels differs. Some panels are recruited from existing lists, such as membership in frequent-flyer programs; this can introduce particular skews in the sample (e.g., frequent flyer club members tend to be wealthier than average). Other panels recruit through a variety of online strategies, including advertisements posted on web pages. It is important to understand how the panel was recruited in order to consider how that may affect the representativeness of the panel.

With all panel recruitment approaches that use online recruitment, the panels are limited to individuals who are online. Although very large and growing percentages of Americans are online (Perrin & Duggan, 2015), poorer, older, and minority individuals are less likely to be online (Perrin & Duggan, 2015), so less likely to be sampled. To avoid this, some companies have constructed consumer panels by first sampling from a non-internet frame, such as address lists, to invite participants into the panel. Those who volunteer but do not have computers or internet access are given a computer and internet service. In this way, panelists can be surveyed online while still sampling people who would not normally be online. Note that there is still a potential bias introduced by the individual’s willingness or unwillingness to join the panel. Regardless how the underlying panel was sampled, the sample for analysis is still subject to non-response bias, due to individuals’ decisions to participate in or decline any particular survey. The bottom line is that no survey sampling method is perfect and completely free of bias.

Practical considerations also enter into the selection of a sampling method or panel. Because any one tobacco product is used by only a small percentage of Americans, surveys must be done with large samples, and may need to be repeated periodically with new participants. This requires the use of large panels. The online panels that are recruited off-line are much smaller than those that use online recruitment. Thus, even if one might consider the off-line-recruitment panels to
be more representative, it may not be practical or even possible to conduct the required surveillance using those panels. Although not perfect, survey panels that recruit online seem like an adequate and appropriate way to collect data about tobacco use.

**Strategic Sampling: User Registries**

Collecting data from a large number of survey respondents can ensure good coverage of broad population segments such as smokers and non-smokers, but it may not provide enough data about the key population that is the focus of surveillance (i.e., users of the index tobacco product). Smoking prevalence is currently estimated at 17% of U.S. adults (Centers for Disease Control and Prevention, 2015). Thus, a product that garnered use by 1% of smokers would thus be used by roughly 1 in 600 U.S. adults. That means that to accrue a sample of 400 users (which constrains the 95% confidence interval of an estimated endorsement of an item to ±5%, and allows for some sub-group analyses among users) would require surveying 240,000 respondents. Even if that were practical for a one-time survey, it is hugely inefficient, and its practicality diminishes quickly when one considers the possible need to repeat the survey periodically with new respondents. This challenge becomes even greater if surveillance is expected to address “products” at a very fine level of detail. If, for example, data were needed on every plausible combination of e-liquid and e-cigarette device as a distinct “product,” the task of finding an adequate sample of product users would become exponentially more challenging.

Other methods are likely to be required to get enough data on users of particular products. Recruitment/sampling methods that specifically target users of the index product are an efficient way to collect data on users. For example, recruitment solicitations can be placed on or in the product packaging, offering compensation to join a specialized research panel or registry of users. As in recruitment to any research panel or study, there may be bias in the self-selection decision by users to join or not join the panel. It may be possible to mitigate any such biases by weighting, if data could be collected on a broader sample of users who provided basic demographic information, even if they were unwilling to join the panel. While potential biases must, as always, be considered in interpreting such data, the use of such targeted recruitment may be essential if sponsors are to have data from a large enough sample of product users. Such data could serve to simply describe product users and their usage patterns, which is a crucial need; comparisons to other samples would be complicated by differences in sampling methods.

In summary, perfect representativeness of survey samples simply cannot be achieved. Sponsors should, however, be sensitive to sources of bias and aim to minimize or mitigate them, and to take them into account in interpreting the data,
while also taking into account practical considerations necessary to obtain data from an adequate number of people.

**OTHER ISSUES IN SURVEYS**

**Weighting of Survey Data**
Survey samples often do not mirror the demographic profile of the U.S. Certain groups (e.g., young Hispanic males) are often under-represented, due to the selection and non-response biases already discussed. One mitigating strategy is to weight the data to better mirror the target population, essentially treating data from under-represented participants as though that sample were larger (i.e., closer to its real proportion of the population) and, conversely, treating data from over-represented groups as though it came from fewer participants. Survey samples and responses are often weighted on factors such as age, gender, ethnicity, region, and income or education, with the aim of matching the demographics of the U.S. population. The details of weighting, especially when one is trying to weight on multiple variables, are beyond the scope of this paper, but are described in detail in many sources (Centers for Disease Control and Prevention, 2014; Westat, 2015; 2016). One should recognize that weighting cannot necessarily correct all sampling biases – by definition, one is weighting the responses of people who did participate in the survey, so no amount of weighting can bring in the responses of groups that are simply not included in the sample (e.g., in internet-based samples, people who are not online, who may differ from those who are online). Nevertheless, weighting for analysis is best practice in survey research. In reporting survey data, the weighting scheme should be clearly described, and it should be clear when weighted estimates are being used.

**Response Bias**
A particular challenge in surveys aiming to detect inappropriate use of tobacco products (or its absence) is the potential that individuals who are engaging in proscribed behavior may be inclined to decline survey participation or be less than truthful about their behavior. As social norms against tobacco use grow stronger, survey respondents may understate their tobacco use, in order to avoid providing what may seem like a socially undesirable response. It has been noted, for example, that estimates of U.S. cigarette consumption based on survey estimates of smoking prevalence and average cigarette consumption fall far short of actual cigarette production and sales (Warner, 2016). People are smoking cigarettes they don't admit to smoking on surveys. As norms and laws against tobacco use by underage youth grow stronger, survey data on use may under-estimate actual use. This potential bias cannot be completely eliminated. Guaranteeing anonymity to survey respondents, and wording questions in non-judgmental ways that encourage truth-telling can help.
Governments Surveys on Tobacco
The foregoing assumes that surveillance data would come from special surveys fielded by the regulated company for that purpose. However, there are also many existing, independent sources of survey data about tobacco use. The U.S. government fields multiple surveys that ask about tobacco use, including the National Health Interview Survey (NHIS) (https://www.cdc.gov/nchs/nhis/), National Health and Nutrition Examination Survey (NHANES) (http://www.cdc.gov/nchs/nhanes/), the National Youth Tobacco Survey (NYTS) (http://www.cdc.gov/tobacco/data_statistics/surveys/nyts/), the Health Information National Trends Survey (HINTS) (http://hints.cancer.gov/), and, most prominently the PATH study (https://pathstudyinfo.nih.gov/UI/HomeMobile.aspx). These are often considered gold standards in their field, and are marked by careful survey development, sampling, and weighting. All of them make their data publicly available. However, there is typically a years-long delay between data collection and release of the data, making them less useful for timely surveillance. Also, with the possible exception of PATH, their questions about tobacco use are quite general and usually do not allow identification of specific tobacco products by brand and style. PATH, which is sponsored by the CTP, has by far the most detailed questioning about tobacco use, and includes detailed queries about multiple tobacco products. PATH also collects biological specimens and analyzes a range of tobacco-related and health-related biomarkers. Even if not perfect, these surveys are considered authoritative, and an important source of information about tobacco use. Where possible, sponsors should consider comparing their samples and findings to those from these authoritative government surveys.

TRACKING SAFETY AND PRODUCT-RELATED ADVERSE EVENTS

Spontaneous Reporting Systems
The FDA requires pharmaceutical companies that market prescription or over-the-counter medications to collect and report adverse events reported by users of their products, regardless of whether the report is actually related to use of the product. Adverse event reporting is done through the FDA’s Adverse Event Reporting System (FAERS) (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/). The information that the FDA has provided with regard to tobacco product adverse event reporting closely mirrors the expectations for pharmaceutical products (U.S. Department of Health and Human Services, 1992; U.S. Department of Health and Human Services, 2009; U.S. Department of Health and Human Services, 2013).

Such “spontaneously reported” adverse events may come from users/consumers themselves, from health care professionals, or from other sources. It may be quite difficult to draw causal inferences about the relationship between the product
and the adverse event (a user reports nausea and thinks it might be due to the tobacco product, but it could be a stomach virus), but all events are to be recorded, and putative attributions are made subsequently. “Unexpected” events – that is, those that were not known at the time of approval and initial marketing – are of particular interest, because they may reveal important effects of a product that were not evident during limited pre-market testing, but become evident when a much larger and more diverse population is exposed to the product under uncontrolled real-world conditions, which may include modes of use that were not anticipated or intended.

Reports of adverse events experienced with pharmaceuticals can be reported to the manufacturer or directly to the FDA. For a tobacco product, it seems likely that the manufacturer’s consumer complaints telephone line or website may be a likely conduit for such reports. Tobacco product manufacturers should consider how their present system for receiving and addressing product complaint/inquiry reports functions, and whether it has sufficient staff, and adequately trained staff, and support to handle the additional regulatory requirements of reporting of adverse events. There are particular regulations about what constitutes a reportable event, how and when such events need to be reported, and how they are coded and tabulated. There are special requirements for reporting what are deemed to be “serious” events (see U.S. Department of Health and Human Services, 1992; U.S. Department of Health and Human Services, 2009). Regulated companies would be well-advised to become familiar with these regulations and with industry best-practices.

Although adverse event reporting systems such as FAERS are used in tracking the safety of drugs, it is widely understood that such reports vastly under-estimate the occurrence of adverse events, and are also difficult to interpret because of the lack of a reliable denominator; that is, one can count reported events, but one cannot easily turn them into a valid rate or incidence of events. Gross sales are sometimes used to put these event counts into perspective, but the approach is also imprecise. Event counts are also sometimes interpreted in light of comparisons across products in the same class, but such comparisons can also be problematic, because of the many factors that influence adverse event reporting. For example, when an adverse effect of a drug gets attention in the media, reporting rates temporarily spike – clearly a reporting bias unrelated to actual event rates. Specialized statistical methods have been developed for detecting important “signals” embedded in the vast noise of spontaneous reporting data (Dart, 2009; Smith et al., 2008).

Adverse event rates may be even harder to interpret when applied to tobacco products. In the world of pharmaceuticals, some health professionals and patients are accustomed to the idea of filing adverse event reports when they think the event is due to medication the patient is taking. Such reports are more likely to be
initiated when the adverse effect is surprising; people are less likely to report that an old-line antihistamine made them drowsy, since they expect that effect. It is not clear what sort of events users of tobacco products will consider report-worthy. Cigarette smokers may expect that smoking will make their throat feel scratchy, or that long-time smoking may result in morning coughing, perhaps making such events unlikely to be reported. That may also be true when a smoker is diagnosed with lung cancer. On the other hand, an e-cigarette battery that explodes and causes minor injury may well get reported (Kumetz et al., 2016). Thus, the frequency of event reporting may bear little relationship to either the severity or the actual incidence of events captured by such a system. Industry and the CTP will need to become adept at interpreting such data over time and with experience.

Other Sources of Product Safety Data
There are sources other than adverse event reports that bear on product safety. Calls to poison centers are one method of tracking incidents that have generated safety concern (Mowry et al., 2015). As with adverse event reporting, these depend on users’ initiative in making a call, in this case out of concern for safety. It is important to understand that simply counting calls is not an accurate way of tracking harmful exposures. Calls are expressions of concern; only some involve exposures and only some exposures lead to material harm. Poison centers track details of calls, so drilling down can determine whether certain types of harmful exposures are occurring. Visits to emergency rooms can also be tracked, and similarly require drilling down to distinguish a concern from actual harm. Obviously, these sources, while possibly useful for tracking acute and perhaps unexpected harms due to acute exposures or product failures (e.g., swallowing of e-liquids, exploding e-cigarette batteries) are much less useful for tracking long-term harms (e.g., lung cancer) due to chronic exposures.

Long-Term Health Effects
Adverse event reporting involves passive surveillance – simply tabulating events that are reported to the company. More active, systematic, and long-term monitoring of health effects may be necessary in some instances. While the CTP has not yet issued any orders allowing reduced-exposure or reduced-risk claims, the Act gives it authority to do so. Both kinds of claims are subject to periodic review and possible withdrawal of approval. In the case of reduced-exposure claims, the sponsor is expected to collect data to show that the reduction in exposure does result in eventual reduction in risk. Although approval of reduced-risk claims implies that the reduction in risk was already established as likely prior to approval, the CTP may expect to review data to validate such claims in the post-marketing environment.

Discussion of studies to track changes in disease risk is beyond the scope of this paper, but a few points can be made. Assessing the health impact of a tobacco
A product will typically require careful design of large prospective studies of product users and a comparison group. Because most of the diseases caused by tobacco have very long incubation periods, studies of disease endpoints will need to be very long if they are to detect reductions in risk. For this reason, validated biomarkers of disease processes will likely play important roles in such studies. For some disease endpoints, studying populations at high risk may provide information more quickly about the effect on these special populations. For example, individuals who have suffered a heart attack are at elevated risk of having another one, and the risk of repeat MI is also higher for those who smoke cigarettes (Buchanan et al., 2015; U.S. Department of Health and Human Services, 2004). In this population, a reduced-risk product might show reduction in cardiovascular risk in a much shorter time frame, and in much smaller studies. However, the generalization to the population at large could be limited. In any case, companies proposing reduced-exposure or reduced-risk claims will need to think about how to document the effects on disease risk in the post-marketing environment.

**FINAL THOUGHTS**

**Is there scope for industry collaboration on surveillance?**

The regulatory obligation for surveillance clearly falls on individual companies marketing products for which they have sought a marketing order from the CTP. As should be evident from the preceding discussion, the effort required to meet these obligations is very significant. Because surveillance efforts cannot limit their focus to actual users of the index product, the efforts expended by multiple companies will also entail a very substantial amount of overlap and duplication. That is, while Company A is performing surveillance of its Brand Y e-cigarette, and Company B is performing surveillance of its Brand Z e-cigarette, both will need to survey large groups of cigarette smokers, former smokers, and never-smokers. Besides being duplicative, the two parallel programs have some chance of producing confusing results, because they may contradict each other, leaving the CTP to sort out the contradictions. Receiving varying data from multiple surveillance programs will confront CTP with a difficult problem of interpretation: the different pieces of the jigsaw puzzle may not fit well together. Even if relatively consistent, different surveys focusing on different products and populations may not yield a coherent picture of the whole. A larger combined omnibus survey is likely to produce more stable results. Given these circumstances, collaboration on industry-wide surveillance efforts may hold great value, both to CTP and to the industry.

**Conceptual challenges in interpreting product-oriented surveillance in a population framework**

How will product-focused postmarketing surveillance help inform CTP’s mandate to protect population health? It is useful to refer again to post-marketing surveillance mandates imposed by FDA on pharmaceutical manufacturers as a
benchmark or point of reference for surveillance of tobacco products in response to the CTP mandates. In conducting surveillance of medications, sponsors are asked to examine the use of their particular product, and the harms it may impose on those users. Similar product risks could be detected by surveillance of tobacco products (e.g., a particular e-cigarette battery tends to overheat). But, based on its statutory mandate, the focus of the CTP is not just on the health of individual product users, and the effects of the index product, but on protecting the health of the population as a whole, by attending to shifts in population tobacco use. This focus may be in tension with product-focused surveillance. There could be shifts in population-level patterns of tobacco use (e.g., an increase in teen initiation) that cannot readily be attributed to any one product. Particularly when there are multiple products in a class (e.g., multiple e-cigarettes), the effect on population behavior may depend more on the aggregate effects of all the products (e.g., perception of e-cigarettes shaped by multiple advertisements, not any one). Population patterns of tobacco use will also be affected by activities not under any one company’s control, and, indeed, not under the industry’s control, such as tobacco control and public communication activities by governmental and non-governmental actors.

It will be a challenge for both the industry and the CTP to use surveillance data to fine-tune initiatives aiming to improve the health of the population as a whole. In the interim, regulated companies will need to develop substantial capabilities for population surveillance.

References


CONSUMER TESTING TO ADDRESS POPULATION HEALTH STANDARDS FOR TOBACCO PRODUCTS

Geoffrey M. Curtin
RAI Services Company
Winston Salem, North Carolina USA

Abstract
The Family Smoking Prevention and Tobacco Control Act (FSPTCA) gives the US Food and Drug Administration (FDA) the authority to regulate the manufacture, distribution, and marketing of tobacco products. With the explicit goal of protecting the public health, the FSPTCA establishes a framework whereby tobacco products are to be regulated based, in part, on a set of public health and population health standards that require consideration of the risks and benefits to the population as a whole, including both users and non-users of tobacco products. In general, these standards have been described in terms of ‘likelihood of initiation of tobacco use among non-users’ and ‘likelihood of continued use (or quitting) among current users’. FDA has given guidance recommending the collection of such information, through consumer testing, in support of a number of tobacco product regulatory submissions, including substantial equivalence (SE) reports, premarket tobacco applications (PMTA), and modified-risk tobacco product applications (MRTPA). This presentation discusses the development and implementation of consumer testing in the areas of ‘comprehension and perceptions’ and ‘likelihoods of use’, including the practical and conceptual challenges involved in addressing these new standards. In particular and as a specific example, the presentation focuses on consumer testing in support of an MRTPA, which additionally requires testing of consumer comprehension for modified-exposure or modified-risk messaging.

Introduction
The Family Smoking Prevention and Tobacco Control Act (FSPTCA) establishes a regulatory framework whereby a tobacco product manufacturer must consider, and in many instances provide evidence on, the risks and benefits to the population as a whole (including both tobacco users and non-users) that may be associated with a product that is the subject of a regulatory submission. (1) Consistent with this framework, the US Food and Drug Administration's Center for Tobacco Products (FDA-CTP) has adopted a set of public health and population health standards (hereafter referred to as the ‘population health standard’) that may require a tobacco product that is subject to regulatory review to be assessed in terms of its likelihood to increase tobacco initiation among non-users (both never and former users) and its likelihood to increase continued tobacco use among current users. An increase in the likelihood of either of these tobacco use behaviors would suggest the potential to adversely affect the health of the population as a whole.
The collection of evidence to address the population health standard will, in some instances, require a manufacturer to conduct consumer testing, conceptualized here in terms of ‘comprehension and perceptions’ and ‘likelihoods of use.’ To various degrees, consumer testing may be needed to support a substantial equivalence (SE) report, premarket tobacco application (PMTA), and/or modified-risk tobacco product application (MRTPA). For an MRTPA, the need for testing will likely be high, as a manufacturer must provide evidence that the product and its proposed marketing is expected to benefit both individual health and the health of the population as a whole. (2) Studies and analyses needed to support a PMTA will likely be similar to that for an MRTPA, but the evidence threshold differs in that the new product must be found to be appropriate for the protection of public health. (3) In contrast, consumer testing in support of an SE report is only anticipated in the event that a new product has different characteristics compared to the predicate product, those differences are expected to raise different questions of public health, and evidence from consumer testing will address those questions. (4)

Figure 1 provides an exemplar of how consumer testing might be incorporated into a systems approach to address the ‘net’ population health effect that may be associated with, in this case, an MRTP and its proposed marketing. Four types of research are specified, including comprehension and perceptions, likelihoods of use, population modeling, and surveillance/survey research. Consistent with FDA-CTP’s draft guidance on submitting an MRTPA, comprehension and perceptions testing would be expected to demonstrate that consumers sufficiently understand any proposed modified-risk or modified-exposure information; and, that consumers appropriately apply that understanding within the context of total health and in relation to all tobacco-related diseases and health conditions. Evidence that consumers sufficiently understand and appropriately apply the modified-risk or modified-exposure information could be provided, in part, by examining consumers’ perceptions of risk, both in terms of the absolute health risks associated with use of the MRTP and the risks of the MRTP relative to other tobacco products, cessation products, and tobacco abstinence. (2)

Following demonstration of a sufficient level of consumer understanding of the modified-risk or modified-exposure information, and application of that understanding within the context of total health, likelihoods of use testing could be used to project expected use behaviors among tobacco users and non-users (both never and former users), consistent with the population health standard. Such projections may be informative in isolation, but their use as ‘transition probabilities’ (i.e., changes in tobacco use patterns - among current, never and former tobacco users) within the context of population modeling would more closely quantify the expected ‘net’ population health effect of the MRTP, accounting for beneficial and harmful transitions collectively. Such a model could,
for example, estimate differences in mortality (and morbidity) expected to result from changes in tobacco use patterns among a counterfactual population for which the MRTP is available for use (e.g., instead of cigarettes), compared to a base case where it is not available.

Figure 1: Exemplar MRTPA schematic, role of consumer testing in assessing ‘net’ population health effect

Finally, robust pre-market surveillance may, in instances where the product that is the subject of an MRTPA is currently in the marketplace but without the modified-risk or modified-exposure information, provide evidence on tobacco use patterns that is informative with regard to population modeling. As specified in FDA-CTP’s draft guidance for submitting an MRTPA, post-market surveillance data would be expected to provide an assessment of the ‘net’ population health effect resulting from actual changes in use behaviors among tobacco users and non-users following issuance of a risk-modification or exposure-modification order. (2)

The subsequent sections on ‘comprehension and perceptions’ and ‘likelihoods of use’ present the scientific studies and analyses recommended by FDA-CTP for inclusion within regulatory submissions, as well as practical and conceptual challenges likely to be encountered during such testing. As the agency has yet to provide explicit guidance on how to operationalize the numerous outcome measures that a manufacturer is expected to address, the information that follows represents a general overview of the testing that may be needed to support a tobacco product submission, in particular an MRTPA. That being said, the Institute of Medicine (IOM) has issued a comprehensive report that provides recommendations on the studies and analyses needed to ensure an evidence-based evaluation of an MRTP’s likely effect on population health; included are descriptions of methods and best practices for studying risk communication and perceptions. (5)
Comprehension and Perceptions

FDA-CTP’s draft guidance identifies several key areas of investigation regarding the effect of an MRTP and its proposed marketing that the agency must consider when determining whether a product meets the criteria for issuance of a risk-modification or exposure-modification order. (2) Included among these key areas of investigation is the effect that the MRTP (and its modified-risk or modified-exposure information) is expected to have on consumer comprehension and perceptions. And while this draft guidance is specific to an MRTPA, there is the potential that the population health standard will be considered by FDA-CTP when reviewing other types of tobacco product submissions. This would certainly include a premarket tobacco application, or PMTA, and may include an SE report when the product that is the subject of the submission has different characteristics compared to the predicate product that could reasonably be expected to raise different questions of public health. FDA-CTP has provided a summary of ‘not substantially equivalent’ determinations, based in part on findings that a new product has different characteristics than the predicate product and those differences could be expected to raise different questions of public health. (6) Among the examples provided, the addition of menthol as a characterizing flavor to a predicate product that does not contain menthol as a characterizing flavor may lead the agency to request additional evidence on consumer perceptions and likelihoods of use.

An MRTPA is expected to provide evidence that demonstrates consumers not only understand the proposed modified-risk or modified-exposure information, but that those consumers understand the relative significance of the information (i.e., apply understanding of the information) within the context of total health and in relation to all tobacco-related health conditions. For studies and analyses that assess consumers’ ability to apply the information within the context of total health, FDA-CTP has recommended that manufacturers provide evidence on perceptions of the health risks associated with using the MRTP relative to other tobacco products (including within the same product category), cessation products, and quitting all tobacco use. (2)

A general framework for the comprehension studies and analyses recommended to support an MRTPA can be found in guidance provided by the Center for Drug Evaluation and Research (CDER) on label comprehension for nonprescription drug products. (7) Analogous to FDA-CTP’s draft guidance for submitting an MRTPA, label comprehension studies are expected to assess the extent to which consumers understand the information on (nonprescription drug) product labeling, and the degree to which those consumers apply that information when making decisions on product use. Generally speaking, data derived from such studies are not expressly intended to predict consumer behavior, but instead are to be used to identify potential changes in product information that optimize
consumer understanding. Evidence on, for example use behaviors, would be provided through other testing formats (e.g., likelihoods of use, in the case of an MRTP), and only after demonstrating that consumers sufficiently understand the (modified-risk or modified-exposure) information.

CDER guidance recommends that comprehension testing assess consumers’ understanding of the major, or primary, communication message(s), in particular those with the greatest health consequences to the consumer. To the extent possible, target levels of comprehension for each primary communication message should be specified within the study protocol prior to testing. Secondary communication messages (e.g., general health information) may also be assessed, but do not require pre-specified comprehension levels. In addition to identifying communication messages and target levels of understanding, study protocols for comprehension testing should specify for demographically diverse populations, with sufficiently large numbers of subjects to evaluate primary outcome measures among important subgroups (including low literacy); employ study designs that adequately address experimental objectives; include questionnaires that target communication objectives; and, minimize factors that may contribute to bias.

Study and questionnaire design should reflect the communication objectives, as well as address the issue of self-selection, i.e., the decision by a consumer to use (or not use) a product based on his or her reading and understanding the product information and his or her application of that information within the context of personal experience. This is particularly relevant with regard to testing in support of an MRTPA, whereby a manufacturer would be expected to include within the study population those consumers for whom the messaging is specifically intended (e.g., tobacco users), as well as those for whom the messaging is not intended (e.g., tobacco non-users) and whose use of the product could adversely impact the overall health of the population. Lastly, the questionnaire should include questions that optimize the validity and interpretability of the information collected; in particular, questions should be designed to assess the specific communication objectives, use simple vocabulary, and be unambiguous and precise (i.e., each addressing a single item or issue).

FDA-CTP’s draft guidance for submitting an MRTPA further recommends that manufacturers provide information from studies and analyses that examine consumers’ perceptions of the health risks associated with using the modified-risk or modified-exposure product, both in terms of absolute risks and risks relative to other tobacco products (including within the same product category), cessation aids, and quitting all tobacco use. (2) As discussed in greater detail within the IOM report on MRPT testing, risk perceptions are central to most theoretical models of health behavior and behavioral decision making, with some indication that
perceptions of the risks (and benefits) associated with tobacco product use have different implications for product use among dissimilar population subgroups. (5)

The collection of data on risk perceptions can likely be conducted in a manner that also provides evidence on whether consumers appropriately apply product information within the context of their total health and in relation to all tobacco-related health conditions. Assessments of consumers’ perceptions regarding the absolute health risks associated with use of the MRTP would constitute an additional measure on whether consumers sufficiently understand, and appropriately apply, the product’s modified-risk or modified-exposure information. Furthermore, assessments regarding the health risks presented by the MRTP relative to other tobacco products, cessation aids, and quitting all tobacco use would inform on whether consumers have misinterpreted the risk information, believing for example that tobacco products within the same category as the MRTP also present less risk and/or the MRTP presents comparable risk to quitting all tobacco use. Widespread belief among consumers that, for example, use of the MRTP presents a comparable risk to quitting all tobacco use would have the potential to adversely affect population health, based on the concept that risk perceptions are central to behavioral decision making.

Likelihoods of Use
Likelihoods of use testing would provide evidence that addresses, either directly or indirectly, a number of key areas of investigation regarding the effect that the MRTP and its proposed marketing may have on population health. (2) More specifically, likelihoods of use testing would directly address the effect that the MRTP is expected to have on tobacco initiation among non-users, including both never and former users, and continued tobacco use among current users. As previously discussed, projections of product use may be informative in isolation, but could also be used as estimates for changes in tobacco use behaviors (i.e., transition probabilities) within the context of population modeling to quantify the expected ‘net’ population health effect of the MRTP. That would address a key investigational outcome by accounting for beneficial and harmful transitions collectively.

Outcome measures recommended by FDA-CTP for examining the likely effect of the MRTP and its proposed marketing on tobacco use behaviors among current tobacco users include likely rates of product use. (2) In particular, use rates among current tobacco users who would have continued to use a product that presents higher risk (e.g., cigarettes) but instead switch completely to using the MRTP; this would, to a significant extent, represent the maximum benefit to the population as a whole. An additional measure of interest would be consumers' use of the MRTP in conjunction with other tobacco products (e.g., cigarettes), which in turn could limit the population health benefit expected with the product and its proposed
marketing. FDA-CTP also suggests that manufacturers provide evidence on the likelihood that current tobacco users who adopt the MRTP will switch to, or switch back to, tobacco products that present higher levels of individual risk; and, the potential for abuse and/or misuse among MRTP users (e.g., assessed in terms of abuse liability). (2) To a significant extent, the manner in which the MRTP is used by current (and future) tobacco users establishes the maximum population health benefit that may be expected.

The second critical population of interest is non-users of tobacco, including both never and former users. FDA-CTP recommends that an MRTPA provide evidence on the likelihood that those consumers who have never used tobacco, in particular youth and young adults, will initiate use of the product; and, that those non-users who adopt the product will switch to other tobacco products that present higher levels of individual risk. (2) The agency also expects evidence on the likelihood that former tobacco users will re-initiate tobacco use with the MRTP. These likelihoods of use projections, i.e., among never and former users, would inform on the unintended consequences that may be associated with the MRTP and its proposed marketing. Increased MRTP use among non-users of tobacco products could reduce the population health benefit expected with increased use of the MRTP (e.g., product switching) among current tobacco users.

The IOM report on MRTP testing suggests examining likelihoods of use based on, for example, intentions (e.g., intentions to try the MRTP) and/or outcome expectancies (i.e., attitudes that are formed by previous knowledge, beliefs and experiences, and that guide behaviors). (5) Suggested questions for measuring intentions to use the MRTP include those that are based on likely use within a specified time frame (e.g., the next 6 months, or lifetime); how the product would be used (e.g., to help quit smoking, or in addition to other products); and, situational conditions (e.g., would use if best friend offered). MRTPA draft guidance provided by FDA-CTP suggests that evidence from consumer perceptions testing (previously discussed) may also be used to inform on likelihoods of use, whereby positive attitudes (i.e., lower perceptions of risk) among consumers with regard to the product would be expected to increase that product's trial. (2)

**Practical and Conceptual Challenges for Consumer Testing**

Practical and conceptual challenges exist with the development and execution of consumer testing, in particular the testing expected to be provided in support of an MRTPA. Foremost among these challenges for an MRTPA is the development of evidence-based information that is sufficiently understood by consumers (including those with low literacy) and does not lead to misperceptions with regard to the health benefits and risks that are actually associated with the product’s use. One approach in the development of product information on reduced risk or reduced exposure would entail the use of qualitative research, including the use
of focus groups, that consists of consumers for whom the messaging is intended (e.g., current tobacco users, including those not intending to quit tobacco use) and not intended (e.g., those consumers currently not using tobacco products, and for whom use would have an adverse effect on population health). Additional research could be used to refine the messaging to, for example, optimize comprehension among the subgroups of interest.

Manufacturers will then need to develop and/or identify measures and/or questions that assess comprehension and perceptions and likelihoods of use for the MRTP and its proposed marketing, consistent with the evidence needed to address the population health standard. In some instances, these measures (and/or questions) may not exist and will need to be developed, or modified to be, specific to the MRTP and its proposed marketing. It will also be necessary to demonstrate the validity of the newly developed or modified measures (and/or questions).

To address the large number of outcome measures and subgroups of interest for which evidence is expected to be collected consistent with the population health standard, a manufacturer will likely need to survey large samples of consumers that represent the US population in terms of demographics and tobacco use behaviors. While opt-in panels may not be fully representative of the US population (e.g., not all have internet access or join online panels), they do allow for the collection of data among sufficiently large samples of consumers (including subgroups of interest, such as young adults, racial/ethnic minorities, and those with low literacy) to support strong inferences on measures associated with consumer understanding (and application) of reduced-risk or reduced-exposure information and subsequent projections of likely use.

When identifying and selecting among existing panels for consumer testing, an important consideration should be the potential for ‘saturation’ among some commonly used sample sources, whereby over-use may lead to a more educated sample with respect to tobacco products and thereby impact study findings. Conversely, those who develop their own panels for testing may need to account for the fact that conducting research among consumers who have little to no knowledge or experience with tobacco products may also affect study findings, since survey participants may be reacting to the product information with minimal to no context. This may be particularly relevant given the prevailing consumer misperceptions with regard to the health risks associated with currently marketed tobacco products (e.g., non-combusted versus combusted), and nicotine in general. In some cases, product information may be at odds with consumers’ pre-existing beliefs; so while the product information may be understood, claims made for the product (e.g., presents less risk compared to cigarettes) may not be believed and could lead to biased responses.
Finally, it must also be appreciated that the studies and analyses expected to support, for example an MRTPA, are by design conducted in an artificial context. Most notably, single exposure to presumably new product information during the course of a research study is not likely to have the same effect as compared to repeated exposures of the information. Repeated exposures would likely lead to improved comprehension of product information, more accurate perceptions of the absolute and relative health risks, and better informed projections of likely use. The decisions made by a manufacturer with regard to product information, measures and/or questions that will be used to assess outcome measures, sample populations (including subgroups of interest), and the context in which the testing is conducted will all impact the interpretation of study findings. These decisions will have to be made and communicated prior to consumer testing, in the form of study-specific testing protocols.

**Discussion**

The regulatory framework established by the FSPTCA, new to both the tobacco industry and regulators alike, requires a tobacco product that is the subject of regulatory review to be assessed according to the population health standard. To address this standard, a tobacco product manufacturer is expected to submit, and FDA-CTP consider, evidence on the risks and benefits of a product to the population as a whole, including both users and non-users of tobacco products. As a practical consideration, the level of consumer testing needed to assess a product’s likelihood to increase tobacco initiation among non-users and its likelihood to increase continued tobacco use among current users will likely vary, depending on the type of submission. Consumer testing in support of an MRTPA is anticipated to be the most rigorous, as supporting evidence is expected to demonstrate that the product and its proposed marketing is likely to benefit both individual health and the health of the population as a whole. Testing needed to support a PMTA will likely be similar, but with a different evidence threshold, *i.e.*, the new product must be found to be appropriate for the protection of public health. In contrast, testing in support of an SE report is only anticipated in the event that the new product has different characteristics compared to the predicate product, those differences are expected to raise different questions of public health, and evidence from consumer testing will address those questions.

The collection of evidence to address the population health standard will likely include consumer testing, which can be operationalized in terms of ‘comprehension and perceptions’ and ‘likelihoods of use.’ Manufacturers who submit, for example, an MRTPA are expected to provide evidence demonstrating that consumers not only understand product information on modified risk or modified exposure, but that they understand the relative significance of the information (*i.e.*, apply understanding of the information) within the context of total health and in relation to all tobacco-related health conditions. For the latter,
FDA-CTP has recommended evidence be provided on consumer perceptions of the health risks associated with using the MRTP relative to other tobacco products, cessation products, and quitting all tobacco use. Additional studies and analyses examining likelihoods of use would inform on the likely effect that the MRTP and its marketing (i.e., reduced-risk or reduced-exposure information) will have on tobacco initiation among non-users, including both never and former users, and tobacco use among current users. These projections of likely use could then be used within the context of population modeling, to assess the expected ‘net’ population health effect of the MRTP and its proposed marketing.

There are a number of practical and conceptual challenges that exist with the development and execution of consumer testing, in particular that testing expected to be conducted in support of an MRTPA. These would include development of evidence-based information that is sufficiently understood and applied by consumers; identification and/or development of valid measures and/or questions that allow appropriate examination of consumer comprehension, perceptions, and likely use behaviors associated with the MRTP and its proposed marketing; and, identification of representative study samples that are sufficiently large to examine all outcome measures and subgroups of interest. The manufacturer, and the agency, must also be mindful of the somewhat artificial context of such testing, in terms of study conduct and interpretation of the corresponding findings.

Despite these challenges, regulatory pathways described in the FSPTCA provide opportunities for tobacco product manufacturers to develop, and introduce into market, new products that in some cases may lead to lower health risks. FDA-CTP should encourage the development and submission of these products for regulatory review. As draft guidance documents for tobacco product applications are finalized and applications are reviewed, FDA-CTP will have an opportunity to accelerate the reduction of smoking-related morbidity and mortality. Reasonable recommendations, quality submissions, and timely review will help achieve this public health goal.
References

1. http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm237092.htm. Sec. 906(d)(1) states, as follows: “The Secretary may by regulation require restrictions on the sale and distribution of a tobacco product, including restrictions on the access to, and the advertising and promotion of, the tobacco product, if the Secretary determines that such regulation would be appropriate for the protection of the public health… The finding as to whether such regulation would be appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.”

2. http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf. Guidance document (Sec. VI, A) states, as follows: “In determining whether it can issue an order under section 911(g) of the FD&C Act for an MRTP, FDA must assess whether the applicant has demonstrated that the product will or is expected to benefit the health of individuals and the population as a whole. In order for an applicant to demonstrate that its product meets the criteria for issuance of an order under section 911(g) of the FD&C Act, the applicant’s MRTPA should address the following key areas of investigation: health risks of the tobacco product; the effect the tobacco product and its marketing may have on tobacco use behavior among current tobacco users; the effect the tobacco product and its marketing may have on tobacco use initiation among non-users (both never users and former users); the effect of the tobacco product’s marketing on consumer understanding and perceptions; and, the effect the tobacco product and its marketing may have on the population as a whole.”

3. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulations Guidance/UCM273425.pdf. Guidance document (Sec. VI) states, as follows: “The information provided in the application described in section V.A of this guidance should present data and information sufficient to enable FDA to make a finding that the marketing of a new tobacco product is “appropriate for the protection of the public health” (section 910(c)(4) of the FD&C Act). The statute provides that the basis for this finding shall be determined: with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.”
4. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM239021.pdf. Guidance document (page 8) states, as follows: “It is important, therefore, that you submit sufficient information to enable FDA to determine whether the new tobacco product has the same characteristics (defined as the materials, ingredients, design, composition, heating source, or other features of a tobacco product) as the predicate tobacco product, in accordance with 910(a)(3)(A)(i), or has different characteristics but it is not necessary to regulate the product under section 910(c)(1)(A)(i) because it does not raise different questions of public health, as required by 910(a)(3)(A)(ii). FDA understands this to mean that 905(j) reports are to be organized based upon the list of characteristics as set forth in section 910(a)(3). In addition to these characteristics, for products that have different characteristics, FDA may determine that additional information is needed to determine whether the products raise different questions of public health.”


INFORMATION FOR ORDERING PREVIOUS SYMPOSIA

FREQUENCY: Annual. One volume per year.

PUBLISHER: The Tobacco Science Research Conference (TSRC) [formerly Tobacco Chemists’ Research Conference, TCRC]

ORDER FROM THE DISTRIBUTOR:
North Carolina State University
University Communications - Customer Service
Campus Box 7603
Butler Communications Services Building
Raleigh, NC 27695 USA
Tel: +1/919-513-3125
extension_publications@ncsu.edu

TERMS: 1. All orders MUST be prepaid
2. Invoice sent upon request.
3. Payment accepted ONLY in U.S. currency or with a check drawn on an American bank with the bank’s nine-digit American Banking Association (ABA) routing transit number. Overseas purchasers: Please instruct the bank to include the following information with payment:
   a. Publication being ordered
   b. Number of copies ordered
   c. Correct shipping address.
   Checks without this information will be returned to the bank for instructions, delaying the order. Overseas subscribers may find it helpful for currency exchange reasons to deal with a serials vendor. See our web site for a link to a vendor list.

SUBSCRIPTIONS: Subscriptions are not accepted, since the number of copies available varies by year. However, we will hold copies upon request, pending payment; and a purchase order may serve to reserve orders, which are otherwise filled on a first-come, first-served basis.

BACK NUMBERS: Inquire for availability or see our web site.

REFUNDS/RETURNS: Not allowed.

DISCOUNTS: No multiple copy discount to subscription agents or vendors.

PRICES: 2006 and Subsequent Meetings: Shipments for these meetings include a CD containing Powerpoint slides for presentations from this meeting.
   $100 per volume for U.S. mailing address
   $140 per volume for overseas - surface
   $160 per volume for airmail
Previous Meetings: See web site above for pricing

SHIPMENT: Surface, unless airmail or FedEx shipment is purchased; cost includes postage.

CONTENTS: Each volume concerns a particular topic in tobacco science. A contents list appears at: http://www.cals.ncsu.edu/agcomm/rats_2006_contents.html
All Recent Advances orders are shipped with the accompanying meeting program booklet, when available.