
# Providing a Science Base for the Evaluation of Tobacco Products

Peter G. Shields MD, Greg Connolly DMD,MPH, K. Michael Cummings PhD, Mirjana V. Djordjevic PhD, Dorothy K. Hatsukami PhD, Jack E. Henningfield PhD, Matthew Myers, JD, Richard J. O'Connor PhD, Mark Parascandola PhD , Vaughan Rees PhD, Jerry Rice PhD, and Mitchell Zeller JD

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Peter G. Shields MD[1], Greg Connolly DMD,MPH[2], K. Michael Cummings PhD[3], Mirjana V. Djordjevic PhD[4], Dorothy K. Hatsukami PhD[5], Jack E. Henningfield PhD[6], Matthew Myers, JD[7], Richard J. O'Connor PhD[3], Mark Parascandola PhD [4], Vaughan Rees PhD[2], Jerry Rice PhD[1], and Mitchell Zeller JD[6]

[1]Lombardi Comprehensive Cancer Center, Georgetown University Medical Cancer, Washington, DC 20057
[2]Division of Public Health Practice, Harvard School of Public Health, Boston, MA 02115
[3] Department of Health Behavior, Roswell Park Cancer Institute, Buffalo, NY 14263
[4] Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD 20892
[5] University of Minnesota Tobacco Use Research Center, Minneapolis, MN 55414
[6]Pinney Associates, Bethesda, MD 20814
[7]Campaign for Tobacco-Free Kids, Washington, DC 20005

Correspondence:
Peter G. Shields, M.D.
Professor of Medicine and Oncology
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
3800 Reservoir Rd. NW
LL (S) Level, Room 150
Washington, DC 20057
Tel: 202-687-0003
EMAIL: pgs2@georgetown.edu

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*Special Note:* This report is a working document intended to assist scientists, regulators, public health officials, legislators and the public. It is anticipated that this document may be commented upon and the Framework possibly be revised pending further consideration.

# LIST OF ABBREVIATIONS

BATCO: British American Tobacco Company
EPA: Environmental Protection Agency
FDA: Food and Drug Administration
LSRO: Life Sciences Research Office
PEG: Product Evaluation Goal
PREP: Potential Reduced Exposure Product
SEA: Substantial Evaluation Assessment

## ABSTRACT

**Context:** Tobacco control efforts and product regulation require an independent scientific evaluation of tobacco products, including their design, use and harmful effects to the individual and population.

**Objective:** The National Cancer Institute contracted the Tobacco Product Assessment Consortia (TobPRAC) to develop a scientific framework for evaluating tobacco products. **Design:** An iterative process ensued involving TobPRAC investigators, consultants, a workshop of independent scientists and public health experts, and written reviews. The recommendations for the framework are not intended to substitute for, or pre-empt, any legal standards, but can be used to facilitate those actions. **Results:** A Conceptual Framework for the scientific evaluation of products worldwide, independent of any specific regulatory environment, has four main components involving pre-market, pre-claims, post-market and monitoring evaluations. It includes the use of validated test procedures with particular emphasis on human studies, and a weight of scientific evidence review and risk assessment for population effects. Several pitfalls for implementing a Framework are discussed. **Conclusions:** This paper provides a scientific framework for evaluating all tobacco products. Current knowledge gaps preclude the validation and full implementation of the Framework at this time, although there is value in implementing parts of it. This Framework also helps to categorize and prioritize a research agenda and infrastructure needs.

# INTRODUCTION

Successful tobacco control programs integrate numerous strategies to reduce tobacco use and subsequent disease. These strategies will likely be strengthened by recent passage of a law authorizing the Food and Drug Administration (FDA) to regulate tobacco products (http://www.govtrack.us/congress/bill.xpd?bill=h111-1256). The FDA's authority includes regulating packaging and advertising, mandating performance standards (e.g., design characteristics and emissions), requiring product testing and disclosure, evaluating tobacco manufacturers' health claims for tobacco products, and evaluating how new products contribute to initiation, cessation, and dependence. The goal of this paper is to present a conceptual scientific framework to help guide evaluation of tobacco products in a way that can help guide future public health efforts to minimize the harm caused by tobacco products. Experience has demonstrated the need for government regulation of tobacco products and marketing and for government oversight of the scientific evaluation of these products. The framework presented herein which applies to both existing and new/modified tobacco products, is intended to inform regulatory-decision making, but it is not specifically tied to the new U.S. regulatory environment, and it does not address the legal standards or encompass the full range of considerations that a regulatory agency would take into account. The scientific recommendations herein are not intended to and do not take into account and are not intended to supersede the legal mandate or legal standards that the FDA or other regulatory agencies are authorized or mandated to use. In order to assist readers in understanding the framework presented in this paper, Table 1 provides definitions of key terms.

With the goal of protecting the public's health, tobacco product evaluation must be comprehensive in its approach. The assessment of a tobacco product for human exposure, individual risk and population harm reduction is admittedly a complex scientific challenge, because of limitations in available scientific methods ranging from the laboratory to human biomarker assessments, and in large

part due to the limited ability to integrate various types of data from diverse studies to make specific conclusions, e.g., in a comprehensive assessment. The evaluation of tobacco products also is challenging because harm is a function not only of the toxins delivered by the product, but also of the way products are perceived and used. The latter is affected by characteristics of the product (e.g., its addictiveness and attractiveness) and by what the consumer or potential consumer knows and believes about the consequences of use. Consumer beliefs and behaviors are affected by what is communicated, who is communicating and how the product is promoted. A key challenge is to avoid inadvertent promotion of products that appear to have harm-reduction properties, only to find later (as with the filtered and low-tar cigarettes of the last few decades [1]) that they provide no benefit to health or that any health benefit is minimal in comparison to increased use .

The Institute of Medicine (IOM), and others, have opined that harm reduction is feasible with continued use of tobacco products if the product ". . . lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants." [2-8] The IOM termed such products "potential reduced exposure products" (PREPs). All major tobacco companies, and some small ones, have marketed or now market products that they have identified as PREPs, but none of these products have actually been proven to reduce harm or lower tobacco-related mortality and morbidity. Examples of these include combustible-type cigarettes (e.g., those with special filters or tobacco modified for reduced toxicant yields on smoking machines), cigarette-like nicotine delivery devices that purportedly heat rather than burn tobacco, and smokeless tobacco (ST) products (examples of PREPS are available at www.tobaccoproducts.org). In some cases, the manufacturers have implied or stated that these products reduce exposure and/or risk. The public health dilemma regarding these products is that exposure claims are not independently validated, and even if validated, any reductions in exposure may not necessarily translate into reduced risk and harm. Moreover, the implications for population risk are even more complex, because it is possible that the marketing of PREPs could promote overall tobacco use by delaying quitting and/or promoting dual use

of tobacco products, inducing former tobacco users to resume use, and enticing non-tobacco users to take up the practice of using tobacco.[2,8]

Figure 1 shows how tobacco product assessment can be dissected into three components—namely, exposure reduction, risk reduction for an individual tobacco user, and harm reduction for the general population of tobacco users (and nonsmokers exposed to second hand smoke). It is important to note that achieving one component, such as exposure reduction, does not necessarily mean that this can be equated with individual risk reduction or population harm reduction. Public health protection requires that products be evaluated for all three categories. However, this is a challenge, because research methodologies needed for adequate evaluation within each category may be incomplete and the relationship of each component to the other would need to be established. For example, a tobacco product can be studied for toxicant exposure reduction by assessing biomarkers following smoking fewer conventional cigarettes aided through the use of nicotine replacement therapy (NRT) or smokeless tobacco, but studies linking toxicant exposure reduction to actual individual risk reduction are more difficult to conduct and have some limitations in scope and validity.[9] The difficulty occurs because some tobacco-related illnesses have a long latency so the effects of the tobacco product on health require studies of long duration. Another critical area of limited knowledge is predicting how the consumers are likely to respond to the availability of a new or modified tobacco product and understanding how usage patterns may translate into population risk. For example, if a lower risk product results in fewer smokers quitting or shifting to dual use it is not likely that this will be a net benefit for public health. The proposed schema acknowledges that there may be a situation in which risk is reduced for tobacco users who would not otherwise quit, but that the overall population disease incidence could worsen. To date, no PREP has been sufficiently evaluated as a harm reduction product. Thus, the assessment of PREPs has been limited to exposure reduction without a validated means of linking this to individual risk reduction, much less to population risk reduction.

The proposed framework assumes that various types of tobacco products can exist on a continuum of toxicant exposure, risk and harm (Figure 2). The scheme in Figure 2 parallels Figure 1 indicating that a product might be exposure reducing, but may not be considered risk or harm reducing without adequate scientific evidence. Importantly, it cannot be assumed that a tobacco product at one point on this continuum will necessarily progress along the continuum toward harm reduction. Herein, we do not provide criteria to classify tobacco products on this continuum, and a classification scheme should not be inferred from Figure 2. A classification scheme, however, might be developed some time in the future.

Critical to the understanding of tobacco use and disease risk are human studies; at the present time laboratory studies (e.g., smoke constituent emissions and toxicology assays) only are useful for screening the potential impact of product design changes. Only human studies can assess directly the impact on exposure and disease risk, and so are a critical element of tobacco product evaluation. Because of the long latency of many of the illnesses caused by tobacco use, intermediate biomarkers of disease risk might be considered as proxy measures to predict risk reduction. In principle, a validated biomarker—one correlated with disease risk and where reduction in biomarker levels is associated with reduced disease incidence—could provide a means for evaluating whether a new and/or modified product may reduce future risk of a disease. However, currently while there are validated biomarkers of tobacco toxin exposure,[10,11] valid intermediate biomarkers of disease risk either do not exist, are not fully validated, or relate only narrowly to specific diseases and not the full spectrum of illnesses that one would want to understand in order to judge population risk. Moreover, it is unlikely that any validated panel of biomarkers would be sufficient for evaluating a product's impact on population risk reductions, because individual risk reduction does not inform about how products ultimately will be perceived and used by consumers. A major and critical challenge with current tobacco product assessment approaches is how to integrate disparate types of data (e.g., chemical, toxicological, behavioral, and epidemiological data) and weigh them to formulate conclusions about individual and population risk. Further, there are

several possible pitfalls for implementing a Framework, as indicated below, such as a perceived endorsement by regulators or academia, for the use of a particular tobacco product. As tobacco products are evaluated, communication of parts of the evaluation to the public should be carefully evaluated and limited because of the complexities of interpretation and potential conflicting data that will be weighed against each other. Rather, the Framework, with its various assessments will lead to specific conclusions about exposure, risk and harm reduction potential for tobacco products that could be communicated after the evaluations are completed.

## METHODS

The National Cancer Institute contracted the Tobacco Product Assessment Consortium (TobPRAC) to develop a comprehensive scientific framework for evaluating tobacco products. The TobPRAC is a Consortium of investigators from Georgetown University Medical Center, University of Minnesota, Roswell Park Cancer Institute and Harvard University School of Public Health. A subset of investigators and consultants embarked on a process to develop this Framework and are the authors of this manuscript. The authors and participants were specifically charged to develop a framework independent of a regulatory process, to not recommend policies, and to consider the best methods for evaluating tobacco products even if there may be some issues of feasibility. (Recommendations that may cross the line into policy are noted in the manuscript.) Through a two-year iterative process, experts representing scientific disciplines believed to be important to tobacco product evaluation met several times to discuss how to do a comprehensive product evaluation. A two day workshop with scientists and public health experts was held January 14 and 15, 2009. Those participating in the process did so with the understanding that this work was independent of any regulatory process and with recognition that methods for product evaluation may not fully exist at this time. The participants in the process are acknowledged at the end of this manuscript.

***Principles, Objectives and Future Needs of the Conceptual Framework***

A framework for assessing tobacco products is described below, along with recommendations for the types of scientific studies that would be performed when using this Framework. The intended audience for this Framework is the public health community, scientists and regulators worldwide. It also can help inform the public and media about the complexities of tobacco use, improving public health and regulation. The Framework is built on the following principles:

1. Tobacco use and the attendant harm is a complex issue, encompassing molecular to behavioral phenomena, so that a comprehensive assessment using a variety of scientific methods is needed to evaluate the impact of changes in tobacco products on public health.
2. As any tobacco product design changes might adversely affect an individual's and population health, all tobacco products must be appropriately evaluated.
3. Harm reduction is a potential strategy for improving public health, but only as one part of a comprehensive tobacco control program.
4. This Framework must not subvert or otherwise adversely affect other proven public health methods to reduce tobacco use and harm.

The objectives of the Framework are to:

1. Provide a means for scientifically evaluating all tobacco products, including existing combustible and smokeless products, and PREPs;
2. Provide an evaluation scheme that could be used to improve public health and lead to a decrease in tobacco-related morbidity and mortality;
3. Prevent unwarranted health claims;
4. Minimize consumer misperception about the relative safety of the tobacco product;
5. Provide an early warning for unintended consequences of PREPs;

6. Provide an incentive, or provide a scientific basis to justify a requirement, for manufacturers to replace harmful products with less harmful products; and
7. Provide a construct that could be used to categorize and prioritize research gaps for study.

## PREVIOUSLY PROPOSED PREP ASSESSMENT STRATEGIES

The IOM and others have offered approaches for assessing PREPs, and the World Health Organization (WHO) has promulgated recommendations for evaluation of tobacco products including modified products, i.e., PREPs. Through its publication *Clearing the Smoke: Assessing the Science Base For Tobacco Harm Reduction,* the IOM considered the feasibility for harm reduction through continued tobacco use.[2,3] However, the IOM noted that no PREPs had been sufficiently evaluated to conclude that one or another could decrease risk; the Institute's report also concluded that validated biomarkers could be used to estimate reduced risk and that regulation of all tobacco products is needed to implement a strategy for harm reduction. However, the IOM did not attempt to provide a framework for comprehensively assessing tobacco products or identify studies to be incorporated into a product assessment, or indicate how such studies would be identified, used and interpreted.

In 2003, the World Health Organization's Scientific Advisory Committee on Tobacco Product Regulation (SACTob) issued a statement of principles regarding new and modified tobacco products.[12] They recommended 10 principles and conclusions regarding the types and quality of evidence needed to examine new tobacco products, in addition to examining multiple aspects of new products (e.g., physical chemical characteristics of the product, constituents, and emissions, uptake of toxicants, toxicity, addiction potential, and disease risk). SACTob also noted that claims of reduced exposure or reduced harm should be supported by adequate scientific data provided by the manufacturer and independently verified by an appropriate government agency prior to permitting the claim. The following year, the WHO Study Group on Tobacco Product Regulation (TobReg) issued guiding principles for tobacco

product research and testing, which provided guidance for establishing laboratory capacity meeting the "highest standards of excellence, transparency, reliability and credibility".[13] The document also distinguished research activities from testing activities: the former related to better understanding the nature of tobacco products and their use, while the latter related to repeated examination and evaluation according to standardized methods to assess product performance. A point of note is that research and testing should be interactive, and include assays of product physical characteristics, chemistry, toxicology and human use patterns.

In 2004, with funding by the National Cancer Institute, Centers for Disease control, the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, the workshop "Methods and Biomarkers to Assess Reductions in Tobacco Toxin Exposure" was held to address methods and measures to evaluate PREPs. This led to a publication by Hatsukami and coworkers who proposed a framework for tobacco product assessment consisting of "pre-clinical" laboratory studies, clinical trials and market research, and post-marketing surveillance and epidemiology studies.[14] The focus of this paper was on describing potential methods for evaluating PREPs and assessing consumer perception of health claims. However, Hatsukami et al., did not attempt to provide a detailed framework for evaluating tobacco products and health claims.[14]

The tobacco industry also has been developing frameworks to study PREPs. Under a contract from Philip Morris USA in 2005, the Life Sciences Research Office (LSRO), a non-profit research organization, began the Reduced Risk Review Project. Philip Morris asked it to "develop an approach to scientifically evaluate and assess the risk-reduction characteristics of potential reduced-risk tobacco products (PRRTP)" (LSRO 2007, p. 9; http://www.lsro.org/articles/rrrvw_report_042407.html). LSRO published three monographs: *Scientific Methods to Evaluate Potential Reduced-Risk Tobacco Products* (http://www.lsro.org/articles/rrrvw_report_042407.html), *Biological Effects Assessment in the Evaluation of Potential Reduced-Risk Tobacco Products* (http://www.lsro.org/articles/rrrvw_report_010408.html) and the *Exposure Assessment in the*

*Evaluation of Potential Reduced Risk Tobacco Products*

(http://www.lsro.org/articles/rrrvw_report_040308.html). LSRO's project framework was divided into three phases: testing, comparative risk assessment and decision-making. The framework drew heavily on pre-clinical (laboratory) studies (*in vitro* and *in vivo*) and human clinical studies, with specific recommendations for biomarkers and biological effects assessments to be utilized. Proposing a weight of evidence approach, the framework also recommended laboratory studies before proceeding to human studies. They also emphasized that increased toxicological effects should lead to the re-design or abandonment of a product design change, and that risk comparisons should focus on lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease, at least. Potentially incongruent with a harm reduction process, they wrote that products that might create new toxic exposures and/or increase less common smoking-related illnesses could still possibly be judged reduced-risk. Importantly, the weight given to epidemiological and behavioral studies was slight, and any consideration of consumer perception, abuse liability, or untoward effects in general was placed in post-market considerations, implying that these factors would not be considered as part of the pre-market evaluation or used to support a health claim of a potential risk reduction tobacco product.

The British-American Tobacco Company (BATCO) also developed an approach to PREP evaluations (http://www.bat-science.com/groupms/sites/BAT_7AWFH3.nsf/vwPagesWebLive/F0BF608FFADEBDF7C12574720035A690/$FILE/Gregg%20SRNT%20PREP%20assessment.pdf?openelement). BATCO recommended a PREP assessment that followed a continuum, ranging from technology assessment to product assessment, toxicology testing, early clinical assessment, and long-term assessment. The BATCO authors noted that "[l]aboratory chemical and biological end-point tests provide information on possible mechanisms that facilitate the decision making process. . . ," but that ". . . the overall evaluation is based on a weight of evidence approach in which the most weight is placed on human clinical data." Unlike LSRO, the BATCO group did not find significant utility in animal studies. It should be noted that the BATCO framework, as

presented, does not address important issues such as downstream effects (e.g., re-uptake, initiation and reduced cessation) and gives little importance to the role of consumer reactions to and perceptions of PREPs. Neither the LSRO nor BATCO approaches formally include evaluation of products already introduced into the market.

Importantly, these industry-sponsored frameworks appear to be intended to support exposure reduction claims surrounding the introduction of PREPs and the products themselves, rather than offering comprehensive approaches for evaluating tobacco products or focusing on harm reduction. The tobacco industry sponsored frameworks also failed to address how consumers may perceive and use these products, and how the availability of these new products might ultimately impact population health. Thus, they fail to consider new or modified product usage patterns within the context of all available tobacco products so they can place PREPs in the proper context for evaluation of population risk assessment.

## BRIEF SUMMARY OF RECENTLY-ENACTED LEGISLATION

As previously stated, the framework described here is intended to inform regulatory-decision making, but it is not specifically tied to the new legal standard embraced in the Family Smoking Prevention and Tobacco Control Act (FSPTCA) signed into law in 2009 (http://www.govtrack.us/congress/bill.xpd?bill=h111-1256). Nonetheless, there are provisions in the FSPTCA for which the framework is relevant as FDA implements this new authority. These provisions include:

- *New Product Evaluations*

FDA will evaluate new tobacco products principally under Section 910 of the FSPTCA. New products may be marketed if FDA makes a finding that such marketing "is appropriate for the protection of the public health." The determination will be made "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."

- *Product Standards*

FDA now has the authority to control the content and delivery of any constituent or component of a tobacco product under Section 907 of the FSPTCA. As with Section 910, the standard focuses on FDA making a finding of what is "appropriate for the protection of the public health", considering 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." The overall standard and considerations are similar to what was described in Section 910.

- *Health Claims*

The FSPTCA also authorizes FDA to evaluate all claims for exposure or risk reduction on a pre-market basis under Section 911 of the new law. Under this provision, a company will only be allowed to make a claim if it can demonstrate that the product, as actually used by consumers, will "significantly reduce harm" to individuals, and benefit the health of the population as a whole taking into account both users and non-users of tobacco products. FDA must take into account the unintended population level effects from proposed claims, such as:

- Decreased interest in quitting
- Increased interest in initiating use of the product among ex-smokers and those who never used tobacco products
- The risks and benefits to users of the product compared to the use of NRT and other products designed to treat tobacco dependence

There are additional provisions regarding exposure reduction claims sought by a manufacturer who cannot produce evidence of a concomitant and significant reduction in harm. In these instances, an exposure reduction claim can be approved if a company can demonstrate that a substantial reduction in

morbidity and mortality in individual users is anticipated in future studies, but the company must also present consumer perception data proving that consumers will not be misled into believing that the product is less harmful or presents less of a risk of disease than a currently marketed product.

## OVERVIEW OF THE CONCEPTUAL FRAMEWORK

Figure 3 provides an overview of the proposed Conceptual Framework and its four principal components. Each component has a Product Evaluation Goal (PRODUCT EVALUATION GOAL), as indicated in Table 2. Critical to the understanding of this Framework are statements about the context from which the Framework is formulated; these contextual issues are indicated in Table 3. The four principal scientific components of the Framework are:

1. *Pre-market evaluation* to study tobacco products with new designs and ingredients by comparing them with conventional and reference products for generating more toxicant exposures, fewer toxicant exposures, different types of toxicant exposures, or alter behavioral use patterns;
2. *Pre-claims evaluation* to evaluate proposed health claims, including weighing the scientific evidence using a clearly articulated methodology for evaluating scientific studies and data, and a risk assessment to assess risk and harm reduction;
3. *Post-market* activities to conduct studies of surveillance, epidemiology, consumer use, and intervention trials to assess disease outcomes in order to confirm the pre-market and pre-claims evaluations when expanded to a larger population; and
4. *Monitoring and re-evaluation* to assess changes to the product after marketing and the need for additional studies under the previous three components.

The PRODUCT EVALUATION GOAL defines the purpose of the component, and achieving the goal requires several "Substantial Evaluation Assessments" (SEA), classified by the study type. Although the Framework components in some ways follow a stepwise process, all SEAs within a component are

required if one is to conclude that the PRODUCT EVALUATION GOAL for that component has been met. Hence, depictions of the Framework in the figures denote "and" rather than "or." Some components and SEAs can be carried out simultaneously, although the Pre-Market Evaluation always occurs before other evaluations. However, while the Pre-Claims Evaluation would occur after the Pre-Market Evaluation, the Pre-Claims Evaluation happens only when claims are being considered, even though the product might already be on the market without claims, i.e., in a post-market setting. Although the sequencing of components is not absolute, some SEAs are better informed by the completion of prior SEAs.

To apply the Conceptual Framework, baseline data will be needed for comparison to new products. For the Framework to be implemented for new products, it will be necessary to identify what is considered a substantial reduction of exposure and the sufficiency of the scientific evidence linking that exposure reduction to individual risk and population harm reduction. Substantial Evaluation Assessment criteria must be predetermined, and the criteria might differ by type of product, who uses the product, and how the product is used. The Framework should adequately consider consumer use, abuse liability, and population effects; it also should integrate data from laboratory and human biomarker studies, including clinical trials and epidemiological studies. Further, the Framework needs to consider the heterogeneity among individual and population subgroups (e.g., race, gender, age, smoking history, metabolic capacity, genetics and health status). This is particularly critical if a new product will appeal to a population subgroup that has not shown substantial interest in conventional tobacco use.

Critical to the Framework are the Substantial Evaluation Assessment criteria, which provide the foundation for evaluating various components of the PRODUCT EVALUATION GOAL. These criteria set forth the minimum amount of quantitative data and the quality of the quantitative data that can be used. The Substantial Evaluation Assessment criteria are not a substitute for a regulatory agency's interpretation of the legal or scientific standards it has been legally authorized or mandated to apply. However, the scientific assessments to be made should take place within the context of a lawfully

mandated government regulated framework, one in which the regulatory agency should have available to it an independent panel of experts (unaffiliated with and not funded by industry) to assist its scientific review. Moreover, the Substantial Evaluation Assessment should be decided upon using evidence-based and predetermined scientific methodologies, as well as a predetermined definition of what constitutes substantial reductions for laboratory results and biomarkers. Also, several disease outcomes should be considered, although prioritization for the type of disease (e.g., the ranking for cancer, heart disease, stroke, asthma and addiction) needs to be determined.

# CONCEPTUAL FRAMEWORK COMPONENTS

## *Pre-Market Evaluation*

Figure 4 depicts the Pre-Market Evaluation of the framework. This component occurs before the introduction of tobacco products into the marketplace and includes all products, whether or not they were conceived or developed as a PREP. The PRODUCT EVALUATION GOAL for the Pre-Market Evaluation is "*How does the tobacco product compare with similar conventional and reference products, and does it result in more, less or different toxicant exposure and use patterns than those products?"*

This evaluation, as depicted here, applies to all tobacco products and can inform decisions in a variety of policy contexts. For example, a regulatory authority might use the Pre-Market Evaluation to only allow products to enter the marketplace that have the expectation to reduce exposure, risk and population harm compared to some type of product or products on the market. Or it might be used to ensure that new products that have more exposure, toxicity, risk and/or population harm are not allowed in the marketplace. The policy maker, of course, needs to weigh the strengths and limitations of the research methods available for the Pre-market Evaluation phase. For example, a regulatory agency may implement a policy that new products should deliver lower chemical yields and/or have a lesser toxic effect, e.g., as has been recently done by the World Health Organization for some chemicals

in cigarette smoke.[15] However, it should be noted that this PRODUCT EVALUATION GOAL includes the use of pre-market studies in a broader context than just chemistry studies (i.e., *in vitro* and *in vivo* studies, behavioral studies predictive of how products will be used by consumers). Moreover, we recognize that these pre-market evaluations have not been well-validated for direct extrapolation to human exposure, risk and population harm. Thus, caution is advised for not over-interpreting a policy decision to allow a product on the market that has lower toxicity, for example, to be equated with reductions in human disease risk , unless or until laboratory studies have been validated to do so. There are other limitations for the use of the Pre-Market laboratory studies for extrapolating to human risk and harm. Specifically, it should be noted that many laboratory studies have reported effects for a narrow range of chemicals or disease pathway(s), and so some reduced effect found in these studies might be trivial compared to the total effect of tobacco and tobacco smoke, or there may be worsening effects that are not being measured.

This PRODUCT EVALUATION GOAL in the Pre-Market Evaluation includes the comparison with both conventional and reference products. It is recognized that the conventional products, defined as those most common in the marketplace, can change over time. Thus, to ensure that a changing conventional product does not result in a mischaracterization of another conventional product as a PREP, a stable reference product (e.g., Kentucky reference research cigarettes or smokeless tobacco) also is recommended for laboratory studies. However, the reference products are only useful as controls to assess changes over time, and not to establish a standard for emissions or toxicity.

The comparators for this evaluation are conventional products and reference products within the same class of products. For example, in addition to reference products, new smokeless products would be compared with the most popular smokeless product on the market and combustible products would be compared with the most popular cigarettes on the market. In some circumstances, the most popular product might not be the best comparator, and so it should not be inferred that this could be the only standard.

Although all SEAs are required to inform the PRODUCT EVALUATION GOAL, an initial assessment of laboratory study results (i.e., physical and chemical analyses and *in vitro* and *in vivo* toxicology studies) would be required before testing in human subjects. After this initial safety evaluation, limited human testing could proceed as described below. The data on human use patterns collected from the limited human testing would then inform the operational parameters of additional laboratory testing. This iterative process would be used to support the marketing of a product to current tobacco users without claims and ethical testing for a Pre-Claims Evaluation. The three SEAs within the Pre-Market Evaluation are noted below.

***Design Feature Analysis*.** This Substantial Evaluation Assessment includes the physical design analysis that might impact product performance or perception about product performance. Physical design analysis of cigarettes includes, but is not limited to, tobacco content and blend type, circumference, length, size, filter characteristics, ventilation, paper porosity and resistance to draw for cigarettes. For smokeless tobacco, it would include tobacco content and blend type, tobacco cut, loose tobacco or packed in sachets, moisture and solids content, pH and other tests. Tobacco products with novel designs could necessitate new methods of evaluation of physical properties. Consideration also should be given to additives and delivery mechanisms that might enhance consumer response.

***Chemical and Toxicological Analyses.*** These include studies of the tobacco chemical contents and emissions analysis, and identification or disclosure of all ingredients and additives. For combustible products, chemical analysis of the smoke would be conducted using several smoking machine protocols that address different ways in which the product might be smoked and changes to the emissions that can result from these differences. Currently, the appeal of smoke emissions testing on a smoking machine is to infer human exposure, but this appeal has not been realized through actual study, for example when comparing smokers' exposures to cigarettes with different machine smoking yields.[16] In the U.S., there is currently no recommended smoking machine protocol to assess smoke emissions (http://www.ftc.gov/opa/2008/11/cigarettetesting.shtm). Thus, the choice of smoking regimens still

needs to be determined. Given that no single puffing protocol represents a typical smoker, several smoking regimens would be needed to assess the quantitative and qualitative changes in a range of puffing profiles. Initial human puff profiles could be determined using limited human testing, which would reveal how the physical changes in the PREP affect human use (e.g., puff volumes on the machine might be higher for products that facilitate increasing puff volumes). Methods and limitations for both smoking machine studies, smoking topography, how to reconcile the two and how to conduct cross-comparison smoking regimens have been recently reviewed.[16] *In vitro* toxicology methods and research gaps also have been recently reviewed.[17]

Similarly, *in vitro* and *in vivo* toxicological analyses would be conducted with smoke generated from a smoking machine using a standardized smoking regimen and human puff profiles as above. The *in vitro* assays would include a battery of tests that examine various cell types and modes of action (e.g., cytotoxic, genotoxic and nongenotoxic endpoints). The *in vivo* assays with experimental animal studies would examine different toxicological endpoints (e.g., cancer, cardiovascular and respiratory pathways, and the actual disease endpoints, where possible). This SEA may include reverse engineering to assess the impact of unique features.

***Limited Human Testing.*** There are several goals for limited human testing in the pre-market phase. Limited human testing would typically be short term switching studies to characterize product use and the effects on short-lived biomarkers of exposure. One purpose would be to develop some level of confidence that smoking machine studies effectively compare products of different designs in ways that consumers will use them, at least for short-term use. This testing would assess how smokers will use the product in order to ensure that the product is used as intended and to determine how human exposure to tobacco toxicants might occur, e.g., through human puff profiles of combustible products or how long and the frequency for ST use for chemical and toxicological analyses. Also studies of consumer beliefs should be undertaken to screen for possible adverse effects such as misperception that the tobacco product is a safer or safe product or offers some other improvement, possible issues

related to delayed cessation, dual use of the new product with harmful conventional products, and possible appeal to non-tobacco users. Limited clinical trials might also be called for to estimate nicotine dosing (e.g., mode of delivery, absorbance and factors that might enhance the effects of nicotine) that would provide information about abuse liability; effects on short-term biomarkers of exposure (e.g., exhaled carbon monoxide, cotinine and nicotine); sensory and other subjective responses (e.g., flavor acceptance and withdrawal relief); risk perceptions; and future intentions for use.

## *Pre-Claims Evaluation*

The Pre-Claims Evaluation, shown in Figure 5, focuses on the scientific basis for supporting a health claim for a PREP or other product claimed to reduce individual risk or population harm. For the purposes of this Conceptual Framework, a health claim includes explicit or implied statements and/or information communicated through tobacco product packaging and other marketing techniques, including claims that a product reduces exposure to tobacco toxicants or risk. The PRODUCT EVALUATION GOAL for the pre-claims evaluation is "*Does the product substantially reduce exposure in human studies relating to different disease outcomes that link to individual risk and population harm reduction when compared with conventional products and/or other PREPs?*" It is assumed that any manufacturer's claims would be evaluated for an effect on disease risk harm reduction, and not just confined to the limited scope of a claim, e.g., if the claim is only that the PREP reduces exposure. This Pre-Claims Evaluation also applies to other claims related to a product design change (e.g., fire safety).

It is important to understand that the Conceptual Framework approaches the scientific basis for supporting a health claim independent of any regulatory review or legal consideration that might be associated with a claim or the wording of the claim. (There may be specific regulatory or case-law requirements for when a regulatory agency is authorized or required to permit or deny a claim, based upon the evidence to be considered, the legal weight to be given to different types of evidence and

what a claim can state explicitly or implicitly.) Also important to note is that the Pre-Claims Evaluation involves conducting only human studies, a weight of scientific evidence review by the authorized government agency of all data that includes human and laboratory studies and a risk assessment modeling process; without sufficient human data, the claim is not supportable. Essentially, only human data can substantiate a human health claim; laboratory studies conducted in the Pre-Market Evaluation corroborate and inform what to study in humans. While the identification of sufficient human data occurs in the context of human risk, it might not necessarily require long term epidemiology studies where the outcomes are diseases with long latency (e.g., cancer and cardiovascular disease).

This Pre-Claims Evaluation would require comparison of the product under study with conventional products on the market, and/or other PREPs on the market, as appropriate; in some cases the choice of comparator might be a policy decision. Other PREPs could be the comparator when claims about PREPs are being made comparing one PREP to another or if there is one PREP that is believed to be exposure or harm reducing. However, it remains to be determined how this would be implemented, given that some PREPs may have greater consumer usage but less reduction in exposure than other PREPs. Also, a comparison of reduced exposure via the PREP with smoking fewer cigarettes per day achieved through nicotine replacement therapy or some other method may result in greater exposure reduction, and so the new product should be considered in this context as well.

There are five SEAs within the Pre-Claims Evaluation, and the implementation of these can differ depending on whether the product is already on the market. These SEAs are based on determining substantial reduction in exposure, individual risk and population harm. All SEAs, noted below, would be assessed before making the health claim. The SEAs refer only to PREPs, but other products claiming to reduce disease risk or population harm would be similarly assessed. The SEAs are:

***Human Clinical Trials.*** An essential component of the Conceptual Framework is human studies, specifically clinical trials. At a minimum, these would comprise randomized trials in which tobacco users would be switched to the PREP; the trial would need to be of sufficient scope, quality, size and duration

to conduct the SEA. The actual trial design and the conventional products and/or PREPs used as comparators would vary depending on the PREP and the claim. The number of studies, and their scope, quality, size and duration would depend on whether the product has been on the market; if the product was already on the market and epidemiology studies are available, then the clinical trials assessment could be smaller in scope in order to complement and corroborate the epidemiology data. The weighting of epidemiology studies would depend on how long the product had been on the market and how widely it is used, which will directly impact the statistical power to determine changes in biomarkers or health outcomes. Several trials would be needed in different populations and with complementary or corroborative trial designs (e.g., different types of switching studies that might allow for *ad libitum* use, controlled use and concurrent use of multiple tobacco products). Nicotine dosing is an important component to measure for abuse liability. Abuse liability of a product (or potential for dependence) should be assessed, and it is conceivable that a PREP might reduce some health effects while increasing dependence. The methods and research gaps for conducting human clinical trials, their measures and how to assess abuse liability have been recently reviewed.[18-22]

The duration of the human studies within this SEA should be long enough to demonstrate that the use of the product has stabilized beyond the initial effects and allow for compensation in nicotine absorbance. For example, a product might result in greater puff volume if there is less resistance on draw, but if the product delivers different doses of nicotine than the study subject's usual brand, a sufficient amount of time would be needed to allow the user to compensate for the difference in nicotine delivery. A topography assessment of how exposure occurs (e.g., cigarette puff volume and puffs per cigarette, and mouth time for smokeless tobacco) would be included to adequately characterize how the product is used and confirm that the puff profiles used for the smoking machine regimens in the Pre-Market Evaluation were similar to actual human use. In the trials, unexpected adverse effects (frequency and severity) would be recorded, although this would be limited to signs, symptoms and illness that develop over a short period of time. (Surveillance studies in the Post-Market

Evaluation would monitor for illness with longer latencies.) Within this SEA, consumer perception and abuse liability would be assessed to provide data on the potential effects on smoking cessation and re-uptake of tobacco by former users.

The trial should include a battery of biomarkers to determine the extent of exposure change under *ad libitum* use that are validated as intermediate markers of effect and for reducing disease incidence, although no such markers have currently been validated. The choice of biomarkers would depend on data from the Pre-Market Evaluation in which the critical biomarkers related to exposure were identified. However, biomarkers for complex exposures that are not chemically-specific would be used to ensure that there is not an altered exposure or effect that was not predicted by the pre-market evaluation and not detectable when only chemically-specific biomarkers are used.

***Epidemiological Studies of Products Already on the Market.*** If the product under review is already on the market, epidemiological studies can provide important information about the use and impact of the tobacco product in the natural environment. Moreover, they can overcome the limitation of clinical trials, in which it is unknown how subjects who enroll in the trial would compare with the general population of tobacco users who naturally choose to use the product. The number of epidemiological studies and their scope, quality, size and duration would depend on how long the product has been on the market. These studies would assess adverse events. As soon as is feasible, longitudinal cohort studies of PREP users and conventional tobacco users should be established to observe changes in tobacco use (e.g., if quitting is lessened or uptake is increased), changes in biomarkers over time, effects on co-morbidities and changes in disease incidence. It may be that a product's use would be uncommon enough to preclude epidemiology studies of sufficient size, scope and duration that would be able to support a positive conclusion to a Substantial Evaluation Assessment, but without sufficient evidence of such, a claim may not be sufficiently supported.

Cross-sectional studies can provide quick comparisons for conventional product and PREP users, identify who is using the product (e.g., age, race and persons with co-morbidities, persons who initiate

tobacco use with the PREP and former smokers), and assess an effect on tobacco use (e.g., proportion of PREP users who were former smokers who have resumed tobacco use with the PREP or of people who use multiple tobacco products including a PREP). If a PREP is used widely and for a long enough period to account for disease latency, case-control studies could be used to assess the influence of the use of that PREP on disease.

Several disease endpoints should be studied in this stage of evaluation. Although diseases such as cancer and heart disease have a long latency, one study design can include the assessment of persons with a history of heart disease and the impact on recurrence, which has a shorter latency. In this component, exposures from second hand smoke would be considered.

The battery of biomarkers to assess exposure and intermediate biomarkers of effect needs to be broad enough to assess the range of exposures determined through the pre-market testing and include screening for unknown constituents. The studies should be sufficiently large to statistically assess subgroups of the population to understand population heterogeneity effects of the PREP.

A challenge to epidemiological studies is that products may change more quickly than standard epidemiological approaches can detect and environmental factors including the marketing of other products might influence product use over short time frames. It is important to be able to detect trends of potential health significance in a timely fashion with great sensitivity and identify products at the brand level. This challenge is similar in certain respects to that of monitoring other addictive drug use, which can be influenced by changes in formulation, dosing capacity, image and other factors. For example, a Government Accountability Office Report concerning the OxyContin abuse outbreak around 2000 came to the following conclusion: "current federal surveys do not provide reliable, complete, or timely information that could be used to identify abuse and diversion of a specific drug." Therefore, many new drug products with addictive potential should be accompanied by surveillance approaches that are capable of providing sensitive, timely and accurate information on the potential patterns of use, misuse, abuse and addiction, including addressing populations that are of particular concern. Such

surveillance programs typically include a mix of approaches to detect the potential range of unintended consequences in a timely enough fashion to enable responsive interventions prior to the development of major public health problems. These approaches may include monitoring in school based programs, internet monitoring of websites and chat rooms of potential relevance, reports from treatment providers on potential trends in product use (www.gao.gov/new.items/d04110.pdf*)* and other creative epidemiological approaches.[23,24]

***Weight of Scientific Evidence Review.*** Results from the above SEAs and those from the Pre-Market Evaluation are integrated into a common assessment about the PRODUCT EVALUATION GOAL for the Pre-Claims Evaluation. The use of a weight of scientific evidence concept can have different meanings to different people, and frameworks can differ among regulatory settings.[25,26] As used in this proposed Framework, weight of scientific evidence refers to a transparent pre-established methodology that results in a qualitative interpretation of all available data (rather than some subset of available data). The qualifier "scientific" to the customary weight-of-evidence review terminology is intended to emphasize the precision of the process.

The Conceptual Framework at this time is not borrowing or endorsing any particular weight of evidence method used by a particular regulatory or review agency, nor is it suggesting that its weight of the evidence discussion should displace or supersede any regulatory agency's interpretation of its legal mandate or legal authority. A weight of evidence review, with a causality assessment, was most notably applied in the first Surgeon General's report that concluded that smoking is a cause of lung cancer in men,[27] but whether the methodology applied in the 1960's is still applicable for today's (and tomorrow's) products or for the evaluation of health claims rather than for proving causality needs to be determined. A methodology that applies to a variety of tobacco products therefore needs to be developed, and it is not intended that one should be developed for each particular type of tobacco product or PREP. FDA, the Environmental Protection Agency (EPA) and the National Academy of Sciences have developed methods for weight of evidence evaluations

(http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283)(http://www.cfsan.fda.gov/~dms/hclmgui5.html )( http://www.nap.edu/catalog.php?record_id=366). However, the methods chosen by these agencies differ. In some cases, only human studies are considered of sufficient strength to support a health claim (e.g., by the FDA), while in others, experimental animal studies are expressly considered (e.g., by the EPA). A weighting system for an evidence-based assessment, as proposed by the FDA, includes: ( 1) an assessment of the substance-disease relationship (e.g., for tobacco, this could be the relationship of toxicants to disease); (2) an evaluation of all data; (3) classification of the studies by study design; (4) rating the studies by quality and source of the data; (5) rating the entire body of evidence for quantity, consistency and relevance, and; (6) ranking the strength of the evidence for making the health claim into levels of comfort that would be provided by qualified scientists (http://www.cfsan.fda.gov/~dms/hclmgui4.html). Embedded within the weight of evidence review is a causality assessment, as was done in that first Surgeon General's report and by others.[27-29] There are other important reasons why previously developed weight-of-evidence reviews cannot simply be used for tobacco products. A weight of scientific evidence review for tobacco products would need to consider evaluating a product that harms people when used as intended with little or no positive attributes, and that the risks are substantially greater than typically considered by the EPA or FDA. Also, the review would consider data assessing a reverse dose-response relationship (e.g., does risk decrease following a reduction in exposure of a long-term smoker).

A weight of scientific evidence review for tobacco products will weigh various types of evidence within this component. It will accord minimal weight to laboratory studies, which are used to establish concordance of findings from laboratory studies to human exposure and provide mode of action data. Decisions will be needed on the relative weighing of observational epidemiology studies versus clinical trials and large-scale intervention studies that assess disease outcomes. Each method has its own strengths and limitations. Second hand smoke exposures also would be considered, but that could only happen for products only on the market.

An important difference between existing weight of evidence methods and those for tobacco products from a scientific standpoint is that tobacco smoke and smokeless tobacco products are complex mixtures of thousands of chemicals and toxicants.[30,31] Thus, it is challenging to study these products and determine risk for the complex exposure assessments for which models have been developed (e.g., the environment).[32] Some approaches used for the environmental setting are to provide relative potencies.

A weight of scientific evidence conclusion can be based on a qualitative, semi-quantitative, or quantitative review of data, as determined by the SEAs in the pre-claims and pre-market evaluations. These, in turn, are weighted to develop a qualified conclusion of whether the PREP will reduce individual risk and population harm. For example, the conclusions could be “will,” “probably will,” “possibly will,” “will not,” or "insufficient data for characterization", but these scientific conclusions are not a substitute for the legal conclusion that a regulatory agency must make in evaluating whether to permit a claim to be made. It should be noted that the weight of scientific evidence conclusion is not tailored to the content of the claim, because a claim and consumers’ adoption of the PREP, no matter how narrowly constrained and evaluated for how the consumer will receive the message, may have unintended negative consequences. The claim evaluation is a separate SEA within this component. The weight of scientific evidence review merely assesses the scientific basis for evaluating a claim, but not a legal or policy assessment of whether a claim can be made. It also does not address how any claim will be perceived.

***Risk Assessment*.** Following a weight of scientific evidence review, a risk assessment process can be conducted that would estimate based on modeling a reduction in disease(s) related to the introduction into the market of a product with a new design. The modeling would be separately conducted for current tobacco users and the general population, and would compare the new product to products already on the market and/or other PREPs, as appropriate. The Framework is not adopting any particular existing risk assessment procedure, as this needs to be carefully considered and

developed for PREPs. A risk assessment procedure for tobacco products would identify the most useful human data, which are then extrapolated to smokers and the general population that includes smokers, former smokers, and nonsmokers (e.g., an assessment that includes second-hand smoke exposure). These data allow for the determination of a dose-response relationship and a decreasing dose-response relationship, e.g., what is the risk reduction that occurs through decreasing exposure after conventional use. Through mathematical modeling, this relationship extrapolates the relationship to the general population, accounting for both individual risks to the tobacco user and changes in tobacco use across the general population. Thus, it would use epidemiology and/or clinical studies to estimate risk to individual tobacco users, while only epidemiological studies would assess risk to the entire population (e.g., to include disease risk among former smokers and uptake by nonsmokers and former smokers). It also would account for susceptible populations, if any (e.g., age, co-morbidities, race and/or gender). A hazard assessment would integrate the above information using both the weight of scientific evidence review and the risk assessment. It would also then account for multiple diseases and total mortality. In the absence of human data, a weight of scientific evidence review in the case of tobacco products would preclude proceeding to the risk assessment. This is different from some settings where experimental animal data may be used (e.g., for the EPA and environmental risks), and the mode of action for toxicity is considered in terms of relevance to humans.[33] In the case of tobacco products, PREPs and health claims, the issues of mode of action and uncertainties can be substantial.

Typically, risk assessments contain uncertainties, which are then accounted for by adjusting the model (e.g., through safety quotients). A tobacco product risk assessment, however, will have many unique uncertainties that have not been considered under other contexts. These include, but are not limited to: (1) novel designs for tobacco products that can result in unknown changes in exposure; (2) uncertainties in the quantitative and qualitative shape of the dose-response relationship, and how this might be affected by dual use of tobacco products; (3) unknowns about how a decreasing dose-response relationship will differ quantitatively and qualitatively from the dose-response relationship (e.g., would

the shape of the curve for exposure and risk with decreasing exposure mimic the shape of the curve for the positive dose-response relationship for increasing exposure); (4) unknowns about how the shape of the dose-response and reverse dose-response relationships differ for tobacco users with different tobacco use histories (e.g., heavy smokers, light smokers and long-term smokers); and (5) unknowns about how the heterogeneity of the population would lead to different risks (e.g., race, gender, co-morbidities and heritable traits). Also, it is unknown how the information for different diseases should be integrated to determine an impact on total mortality in a risk assessment process. There are additional uncertainties around the use of exposure and effect biomarkers, specifically how well they estimate subsequent disease risk.

The modeling of complex mixtures, as occurs from tobacco use, has many uncertainties because combined exposures of chemicals can cause additive, synergistic, or antagonistic effects, and experimental animal models do not necessarily provide data that can easily be extrapolated to human risk assessment.[34] Risk assessment methods for complex mixtures have been developed by EPA using relative potencies assessment and toxic equivalences (http://www.epa.gov/NCEA/raf/pdfs/chem_mix/chem_mix_08_2001.pdf) and have been used to rank the relative potencies of chemical constituents of tobacco smoke using EPA cancer and non-cancer slope factors.[35] However, the development of cancer slope factors for applications in the environmental setting may or may not apply to tobacco-related risks, and so whether this concept can be applied to tobacco products and PREPs remains to be determined. How to model complex tobacco use exposures is currently unclear.

A unique aspect of a risk assessment for tobacco products includes an assessment of the risks of many diseases and, for example, balancing the competing risks of increases in some diseases with decreases in others.

***Health Claims and Product Messaging Evaluation.*** This SEA focuses on the nature of the actual claim and the messaging as the consumer may perceive it, and is warranted if the other SEAs in this

component indicate that a claim of some type has a scientific basis. There are several ways that product messaging can be communicated by manufacturers (e.g., explicit health claims via websites, point of sale advertising or other promotions, product labeling or inserts and product packaging) that would need to be considered. The purpose of this SEA is to ensure that consumers correctly understand the health claim so they can make informed decisions about using the product. The type of assessment of consumer perceptions would be influenced by the nature of the claim and manner of communication. Methodologies that have been used for such assessments include focus groups, surveys, human laboratory studies and clinical trials. Key outcomes for assessment include awareness of product, understanding and comprehension of product claims, perception of product risks and benefits, attitudes toward the product and product use, intentions to use the product in the future and anticipated ways the product might be used. For some claims, limited test marketing might be necessary to examine the perception of claims within the broader context of marketing and promotion. This SEA probably will not be applied until other SEAs are completed within this component so that the content of the claim can be considered in the context of other data.

### *Post-Market Activities*

Post-market activities are shown in Figure 6. These activities occur for all tobacco products, whether or not a claim exists. However, if a claim has been made, then the post-market activities need to also assess the impact of the claim. The PRODUCT EVALUATION GOAL for this component is *"Does the product adversely affect consumer use (e.g., initiation, intensity or cessation), biomarkers, and health outcomes on an individual and population basis?"* An important aspect of the post-market activities is identifying unintended consequences of product design changes. The substantial increase or decrease in the evaluation criteria, therefore, is intended to confirm that the product is not adversely affecting public health, to validate the risk assessment model, and to re-assess the validity of

the claim. The post-market activities include different types of study designs. Surveillance studies, epidemiology and intervention trials for disease outcomes (e.g., Phase III clinical trial), as described below, are complementary. There are strengths and limitations of observational epidemiology studies in the naturalistic environment (e.g., effects of unknown confounding variables, duration changing products and behavior and the ability to see the effects for PREPs in persons who dually use both the PREP and conventional products, or have a long history of tobacco use), as there are for intervention studies for disease outcomes (e.g., challenges in choosing and finding controls, changing behaviors of control groups, duration, changing study subjects in each arm over time and compliance).

Difficulties currently exist in conducting post-market activities, because a surveillance mechanism is not currently in place in the United States. Without knowing how a product is changing, and how consumer use of the product may change, data interpretation about individual risk and harm can be hindered. Post-market activities include the three SEAs detailed below.

***Population-Wide Surveillance*** This activity assesses how the product is used and by whom. Thus, it would include surveys about consumer use, perception the impact of the product and the claim, if any, on the use, initiation, dual use, cessation and re-uptake of tobacco use. It also would include changes in exposure to second hand smoke (numbers of people and quantitative levels of toxicants). Within the surveillance studies, which could be enabled through national surveillance mechanisms, the differences in use by such factors as race, gender, age, prior tobacco use history and co-morbidities would need to be assessed. The assessment, however, might be limited in its ability to associate changes due to PREPs against a background of conventional tobacco use. Health claims and product messaging evaluation also would be needed. Some of the research methods and challenges in conducting surveillance around tobacco products has recently been reviewed.[36]

***Epidemiology.*** These studies would be similar to the activities for the Pre-Claims Evaluation; if no claims have been made, this evaluation could be identical to what is described above. Thus, it would include both cross-sectional and cohort studies. If the product has only recently been introduced to the

market, then cohort studies could still be established to assess uptake, use, the effects of the product on biomarkers and effects of second hand smoke. This, of course, depends on the expected wide-spread use by consumers. As noted above, depending on how long the product had been on the market and if its use is widespread, case-control studies can more quickly provide data than cohort studies. The epidemiology studies should be sufficiently large to assess population heterogeneity. Health claims and product messaging evaluation also are needed. As discussed above, given that products are, or may be short-lived on the market, and that product-designs can be changed frequently, novel surveillance methods will need to be developed.

***Intervention Studies for Disease Outcomes.*** Depending on the extent of use, the expectations for the PREP on disease risk, and/or the nature of the claims, large-scale intervention trials can be initiated to corroborate the epidemiology studies. Such trials provide for an experimental design that reduces the chances of confounding and bias that can occur with epidemiology studies. However, depending on the disease outcome, these studies may not be feasible due to the long latency of some diseases or anticipated changes in the design and evolving technologies for a particular PREP. They may, however, be feasible in high risk populations (e.g., persons with cardiovascular disease who cannot or will not quit smoking).

## *Monitoring and Re-evaluation*

Figure 7 depicts the monitoring and re-evaluation activities. This component is described as a distinct component of the Conceptual Framework to denote its importance and critical nature for continuous review of data obtained during post-market surveillance, as well as disclosure of information on the continued evaluation of changing products. The PRODUCT EVALUATION GOAL for this component is "*Has the product been changed, or have there been effects on risk perception, use patterns or health that warrant its re-evaluation?"* This component has three SEAs, as described below.

***Monitoring for Product Design Changes and Toxicant Effects*.** This SEA would involve ongoing disclosure by manufacturers of changes in product design, effects on exposure and emissions in the laboratory and through human studies. Essentially, this evaluation is the re-application of the pre-market analysis scaled by the extent of the product design change and the results of initial screening studies. Substantial outcomes and predicted adverse impacts by changes in product design may result in re-testing the product, withdrawal or modification of a claim, corrective advertising, or complete removal of the product from the market.

***Monitoring of Post-Market Activities*.** This SEA mandates an assessment of the post-market activities and new laboratory and human studies depending on the results of that evaluation (e.g., if the post-market activities indicate use of a PREP that is different than identified in the human studies for the Pre-Market or Pre-Claims evaluations, or if the claim has had some unexpected adverse consequences).

***Re-evaluation*.** Depending on the first two SEAs, it may be necessary to revise the weight-of-scientific evidence review and the risk assessment. New SEAs and predicted adverse impacts by the changes in product design may result in abandoning the sale of the product or withdrawing a health claim. The criteria for triggering a re-evaluation is beyond the scope of this manuscript, but will need to be developed.

## Possible Pitfalls for Implementing the Conceptual Framework and Premature Tobacco Product Evaluation

Tobacco use and its effects on human health are complex. However, the scope of the Conceptual Framework, its many components and identified research gaps should not deter a tobacco assessment process from being comprehensive, as we propose herein. Tobacco products on the market today are dangerous and it is important that a comprehensive evaluation consider all the complex issues associated with this in order to avoid unforeseen adverse consequences. While the Conceptual Framework was developed independent of a regulatory environment, it is intended to provide scientific

assistance to those involved in regulatory decision making process. It does not and is not intended to substitute for the legal standards or policy judgments that guide any regulatory agency.

An additional consideration outside the scientific evaluation proposed in this Framework includes some ethical considerations that balance the risk of consumer misperception and inappropriate use of a new tobacco product versus withholding information from consumers and removing their rationale to switch from their usual and possibly more harmful product.

In the U.S., the recently enacted FDA legislation will lead the FDA to adopt some type of comprehensive approach for the evaluation of tobacco products that will then foster research and the development of an infrastructure for post-market activities. The proposed Conceptual Framework could provide scientific guidance to the FDA as it determines how to apply its statutory mandate, but cannot yet be fully implemented because of some research gaps, infrastructure needs and lack of validation. However, there is value in implementing parts of it pending validation of new research methods, and in specific contexts, with an understanding of the limitations of existing data and the need for caution in reaching conclusions. Potential pitfalls of reaching premature conclusions include a worsening of public health from tobacco-related disease due to widespread use of a product that is no different or perhaps worse than what is currently available; a false sense of security among tobacco control decision-makers; and consumer misperception about the relative safety of a tobacco product, in general, and also which maintains per capita tobacco use because of ineffective communication about the product assessments. Other pitfalls relate to the tobacco industry and the creation of disincentives for real change because a SEA inadvertently focuses research on the wrong or misleading studies, the evaluation criteria are wrong, or that a SEA discourages innovation because of what would be needed to satisfy the criteria. A risk also is that implementation of a framework could be perceived as government and/or academic endorsement of tobacco use or a tobacco industry partnership with government and academia.

## SUMMARY AND CONCLUSIONS

A scientific framework is offered for a science-based evaluation of all tobacco products, including PREPs, in relation to individual risk and population health. It was developed in the context of an endemic public health problem produced by a tobacco product manufacturing industry that has prioritized profits over public health. The framework aims to address the effects of tobacco product design on use and health through a comprehensive scientific evaluation, ranging from laboratory studies to population surveillance. This Framework was developed independently of any regulatory context. It is intended, rather, to provide an empirical basis for product assessment for public health purposes. However, for it to be effectively implemented, there needs to be an independent government agency with regulatory authority and scientific expertise to oversee the process and insure the transparency and integrity of the system. While there are many components to the Framework, and potential pitfalls, this reflects the need to ensure adequate evaluation of a complex public health problem where prior history dictates caution, e.g., assumptions that lowering cigarette tar yields would lead to a less harmful product.

The Framework has four components and each is composed of PRODUCT EVALUATION GOALs and SEAs that lead to conclusions of a substantial change in one tobacco product compared to another (e.g., a conventional product or other PREP). The Pre-Claims Evaluation is a separate process due to its complexity and potential impact on human use and behavior. It requires human studies of sufficient scope, quality, size and duration, as well as a weight of scientific evidence review and risk assessment. The requirement for human studies is typical for some weight of scientific evidence review and risk assessment processes, such as those used by the FDA, and in contrast to others, such as those used by the EPA. However, many aspects of a weight of scientific evidence review and risk assessment are unprecedented because tobacco use is inherently dangerous yet widely used with substantial adverse health effects.

It may be considered that some aspects of the Framework are challenging, e.g., studies that are of sufficient size, scope, quality and duration, because of challenges in conducting switching studies, need for large enrollments and duration in the context of diseases with long latency. The Framework also calls for research methods and tools that in some cases do not yet exist or have not yet been validated. It also may be that some amount of research will fill some research gaps sufficiently to fully implement the Framework. This allows for this Framework to guide funders to establish research priorities. Notably, TobPRAC has recently published a series of papers that provides a critical review of many aspects of tobacco research and components of this Framework, along with the identification of research gaps that preclude the full implementation of this Framework.[16-22,36,37] Baseline data for conventional tobacco products need to be determined for comparator purposes. Additionally, a rich research agenda needs to be identified and implemented into the SEAs of this Framework. Specifically, the scientific certainty of decisions will be improved as more knowledge is developed for: 1) the best ways to characterize toxicant yields in the laboratory mimicking the broad range of human use; 2) identifying a battery of validated biomarkers for disease risk; 3) a better understanding of the impact of complex chemical exposures on human health, including additive, synergistic and antagonistic effects; 4) understanding the relationship for exposure reduction to disease risk, other than for smoking cessation; and 5) developing methods for weighing various types of scientific evidence and a process for conducting risk assessment in the setting of inherent uncertainties. How the data inform the Framework's PRODUCT EVALUATION GOALs and the criteria for the SEAs is another research gap that needs to be developed by a deliberative panel of qualified experts unaffiliated with the tobacco industry. This Framework also can be used to identify infrastructure and resource needs. However, while there may be challenges in the implementation of the Framework, this should not preclude the need to for an adequate and comprehensive evaluation of tobacco products. While this Framework identifies the types of studies that would be needed to comprehensively evaluate tobacco products, the Framework, as currently conceived, is not intended to provide directions on how to interpret data from

tobacco product assessments, nor does it provide methods for integrating disparate data, weighting various types of scientific evidence, or conducting a risk assessment process. These methods remain to be developed and thus are not considered further.

In the United States and worldwide, there are unprecedented opportunities for tobacco control efforts and reducing tobacco-related harm through regulatory actions. If scientific studies are to support evidenced-based decision making by regulatory agencies, then the scientific community must lead this process. Tobacco use and its attendant ill effects are complex, and thus a comprehensive evaluation for all tobacco products using validated test methods are needed that range from the laboratory to the population.

# TABLES AND FIGURES

Table 1: Definitions Used in the Conceptual Framework

| | |
|---|---|
| Claims | Any statements, explicit or implied, about exposure, risk, or harm reduction made by a tobacco company or their representatives of any type (e.g., through advertising, labeling, press releases, public statements, scientific publications and presentations, or messaging). Claims can be written, oral, or visual (e.g., product packaging). |
| Conventional products | The most popular products on the market in a similar class (i.e., smokeless or combustible). |
| Disclosure | This refers to full disclosure of all scientific information that can be conveyed by a tobacco company related to a tobacco product, including the product design and any changes (new and existing products), product content (e.g., additives and suppliers of product components), any and all studies, study results, raw data, methods, protocols and QC data. |
| Exposure reduction | A reduction of tobacco and tobacco smoke toxicants that enter the body, assessed through human studies and generally with biomarkers. Exposure reduction may apply to single toxicants, several, or many as contained in a complex chemical mixture such as cigarette smoke. Note that at this time exposure reduction cannot be extrapolated to individual risk reduction, which is assessed though epidemiology and clinical studies of tobacco users. The term "exposure reduction" only refers to human studies. There are several validated and partially validated biomarkers for exposure reduction. |
| Harm reduction | An overall reduction in tobacco-related disease in the population, which accounts for risk in tobacco users who delay quitting, former users who resume tobacco use, and effects on initiation, which can only be directly measured through epidemiology studies of sufficient scope, quality, size and duration. This may be estimated via risk assessment models that would need to be developed for tobacco-related harm reduction. |
| Laboratory studies | Non-human experiments conducted in a laboratory, although human cells and tissues might be used (i.e., physical analysis and *in vitro* and *in vivo* animal studies). |
| Potential reduced exposure product (PREP) | A tobacco product that potentially reduces a person's exposure to tobacco toxicants, as compared with conventional products. (Non-tobacco PREPs are not considered herein.) |
| Population heterogeneity | Inter-individual variation for the predictors of tobacco use and harm in tobacco use behavior and disease risk within a population (e.g., race, gender, age, co-morbidities, tobacco preference, tobacco use history, and genetic susceptibilities). |
| Product Evaluation Goal (PRODUCT EVALUATION GOAL) | A specified goal for each framework component, as indicated for the pre-market, pre-claims, post-market and monitoring and evaluation components. It consists of several types of "substantial evaluation assessments." |
| Reference tobacco product | Commercially available research cigarettes and smokeless tobacco where the product is well-described and is not changed over long periods of time. |
| Reverse dose-response relationship | Reduction in exposure is correlated with reduction of individual risk and population disease incidence. Although countless epidemiological studies have demonstrated a positive dose-response relation between tobacco use and disease, it may or may not be true that a reduction in exposure would similarly follow qualitatively and/or quantitatively. |
| Risk assessment | A quantitative assessment by modeling of both individual risk and population harm reduction. |
| Risk reduction | A reduction of tobacco-related disease in tobacco users that occurs from sufficient exposure reduction that is measurable in human studies, but only applies to risk for individuals (versus harm reduction that applies to population risks), which is estimated via epidemiology and clinical studies of tobacco users. Biomarkers, if validated in the context of risk and risk reduction, may be used as surrogate intermediate biomarkers of disease risk. |
| Substantial Evaluation Assessment (Substantial Evaluation Assessment) | Qualitative evaluation of the quality and quantity of quantitative data targeted to answering product evaluation goals, leading to an affirmative or negative decision on whether the product has changed in relation to the product evaluation goal, considering exposure, risk and harm. It might be an evaluation of decreases in human exposure, risk and harm. Thus, the substantial evaluation assessment determines if there is the minimum amount of data needed to affirmatively answer the product evaluation goal or refute it. |
| Substantial reduction | Clinically meaningful changes in exposure, risk, or harm reduction (e.g., that affect human health where statistical significance would not be the only criterion). |
| Weight of scientific evidence review | A qualitative assessment using an established scientific method overseen by an industry-independent scientific process (e.g., governmental or authoritative agency) for addressing the product evaluation goals posed in the Conceptual Framework for the pre-claims evaluation. |

## Table 2: Components and Product Evaluation Goals of the Conceptual Framework

| | |
|---|---|
| Pre-Market Evaluation | How does the tobacco product compare with similar conventional and reference products, and does it result in more, less or different toxicant exposure and use patterns than those products? |
| Pre-Claims Evaluation | Does the product substantially reduce exposure in human studies relating to different disease outcomes that link to individual risk and population harm reduction when compared with conventional products and/or other PREPs? |
| Post-Market Activities | Does the product adversely affect consumer use, biomarkers and health outcomes on an individual and population basis? For PREPs with claims, do intervention studies support the claims for disease outcomes? |
| Monitoring and Re-Evaluation | Has the product been substantially changed, or are there potential unanticipated uses/effects that warrant re-evaluation? |

Table 3: Contextual Issues for the Conceptual Framework*

| Contextual Issue | Explanation and Relevance |
|---|---|
| Application of the Framework to a regulatory environment | This Framework was not developed exclusively for a regulatory perspective; it applies to regulated, semi-regulated, or unregulated environments, and so takes a broad science focused public health perspective that is not always consistent with a regulatory process (e.g., one that considers mandated legal standards and may consider public health, economics and politics for making policy decisions). |
| Application of the Framework to the type of tobacco product | The Framework is applicable to all types of tobacco products, whether the product is intended to be a PREP or only later considered to be a PREP; it includes any product that contains tobacco. |
| Types of studies used to support health claims | It is a fundamental component of the Framework that only human studies and associated data can be used to evaluate human health risk and to support human health claims. However, this context does not negate or minimize the need for laboratory studies, which are used for understanding mechanisms, screening assessments of product design changes, informing the design and components of human studies, and assessing potential worse effects. |
| Types of human studies used to support health claims | Only human studies of sufficient scope, quality, size and duration to assess perception, use, abuse liability, biomarkers and other aspects that might enhance a harm reduction assessment should be used. Both epidemiology and clinical trials would be used; the scope, quality, size and duration of the clinical trials depend on the available epidemiology; more extensive trials are needed if there is limited or no epidemiological data because the product is not yet on the market or has only been on the market for a brief period of time. |
| Types of research methods used for implementing the Framework | Only validated research methods will be used in the Framework, generating data that will not be misused by the tobacco industry or misinterpreted by the public. |
| Who does the Framework apply to? | The Framework applies to any tobacco user, although it would be tailored to the type of tobacco used and who and how many people use it. The Framework must consider the impact on all stages of tobacco use, from youth contemplation, smoking initiation and transitions from experimentation to regular use. |
| Who will conduct the studies that inform the Framework? | Tobacco manufacturers will be responsible for conducting or funding many of the studies, with full disclosure of all study design, execution and data. Academia, governmental agencies, or other independent entities not funded by industry will provide an independent assessment limited to verifying key industry data, which will be done with adequate funding. |
| Can the Framework be implemented? | It may be that not every component of this Framework can be fully implemented today, because there are insufficient or not yet validated scientific methods to develop all of the data, including the methods for weighing evidence and risk assessment. Also, without a regulatory environment, no mechanism exists to ensure full disclosure by tobacco companies. Although the Framework is likely not fully implementable today, sufficient methods are available to conduct partial assessments and draw conclusions about new tobacco products and exposure reduction. |

* Some of the contextual issues span the interface between scientific considerations and policy; where possible, we have tried to address this by limiting the Framework to the former.

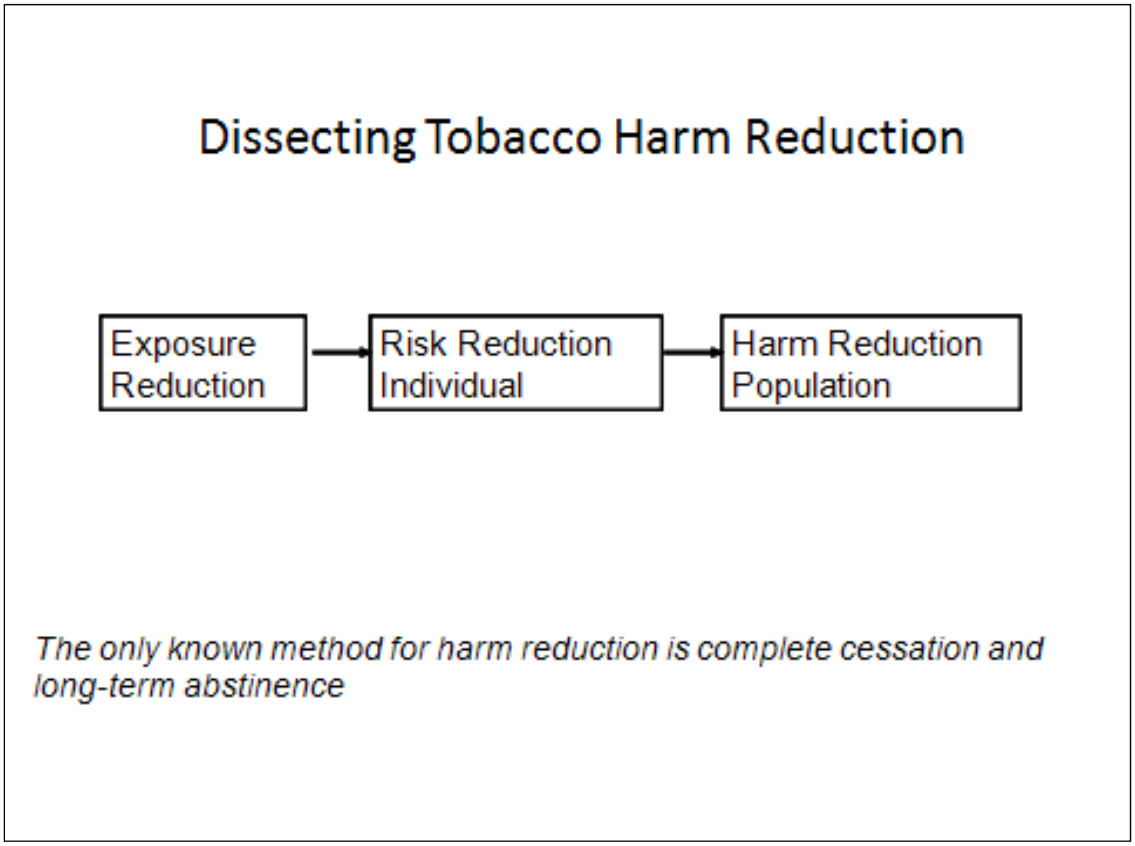



Figure 1. Dissecting Tobacco Harm Reduction

Harm reduction is conceptually separate from exposure and risk reduction, and the linkages among the three elements have been incompletely evaluated. Methods now exist to assess exposure reduction through biomarkers, but how these relate to risk reduction has been incompletely studied; for example, there are no sufficiently validated biomarkers of cancer risk. Although epidemiology studies might indicate risk reduction for current tobacco users after switching to a PREP, this may or may not reduce disease incidence in the population, depending on changes in overall tobacco use. Figure 1 adapted from Hatsukami, et al, 2009.

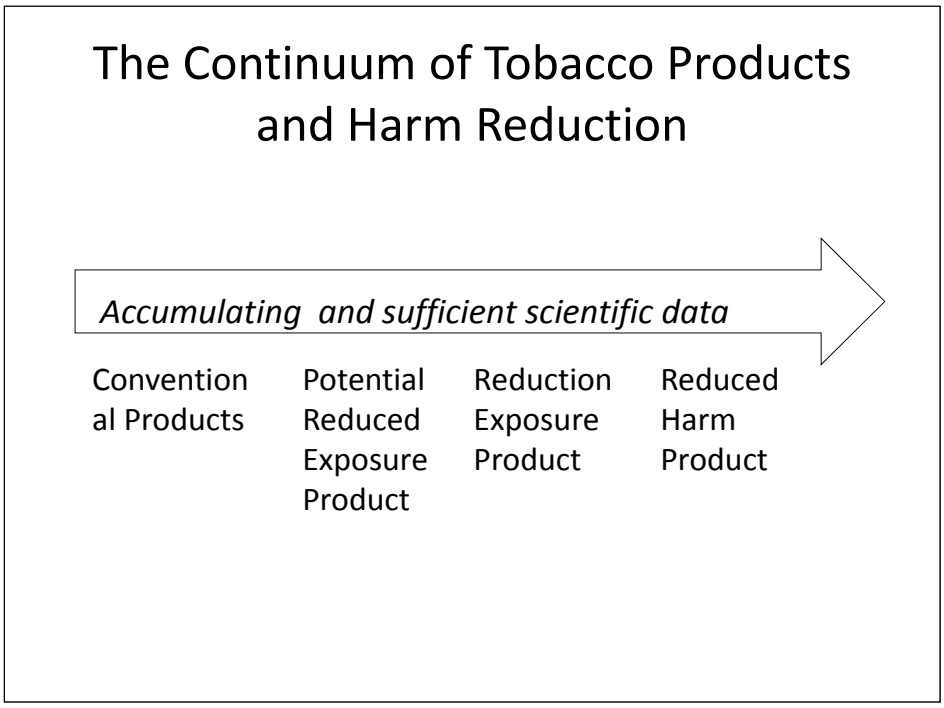



Figure 2. **The Continuum of Tobacco Products and Harm Reduction**

Tobacco products may be conceptually considered as conventional existing products; PREPs; or—after sufficient scientific evaluation—a reduced exposure product. After further evaluation and full implementation of the Framework, a product might be considered a reduced harm product. This figure is not meant to imply a classification scheme.

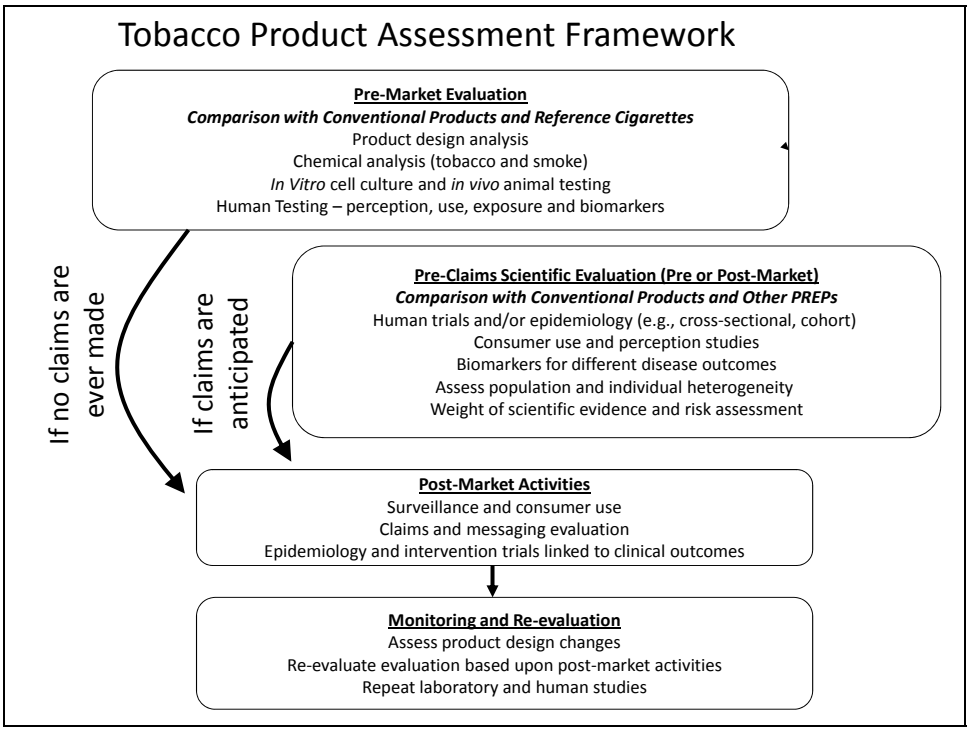
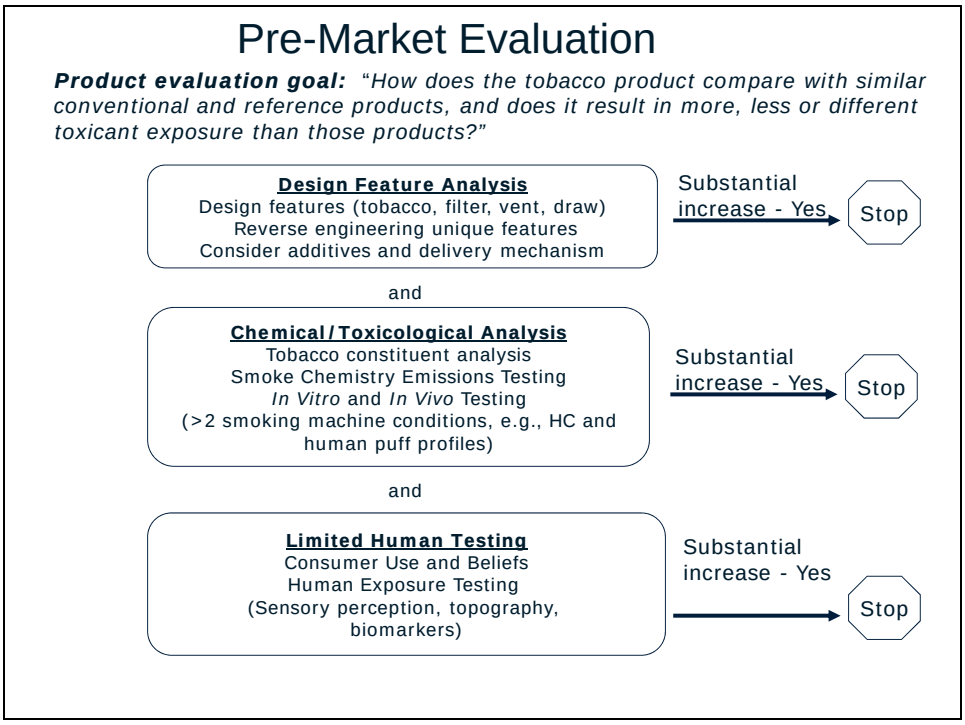



Figure 3. **Tobacco Product Assessment Framework**

The Conceptual Framework proposed in this report comprises four components, each of which includes a Product Evaluation Goal and several Substantial Evaluation Assessments.




## Figure 4. Pre-Market Evaluation

The pre-market evaluation component includes three SEAs. HC, Health Canada method for smoking parameters on a smoking machine.

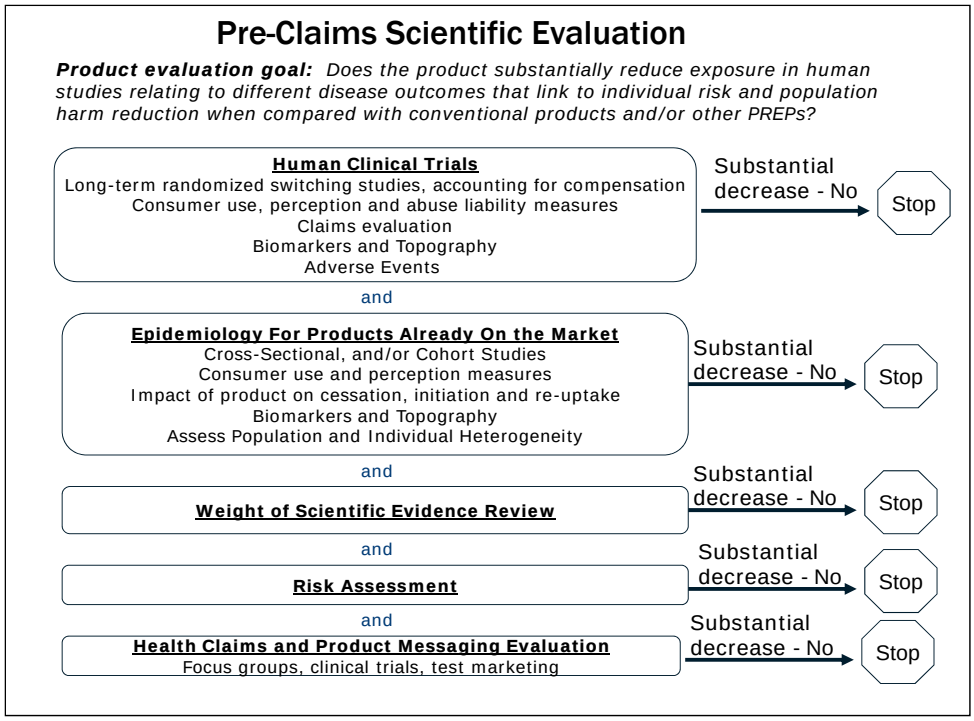



Figure 5. Pre-Claims Scientific Evaluation

The pre-claims scientific evaluation component includes five SEAs.

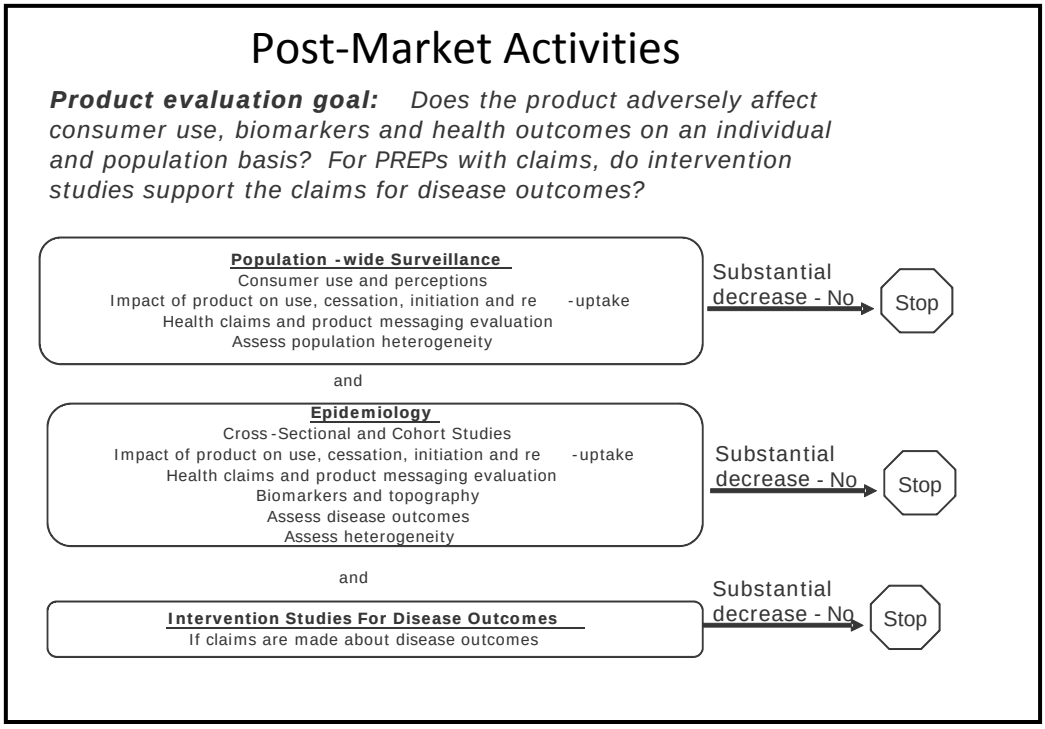



Figure 6. **Post-Market Activities**

The post-market activities component includes three SEAs.

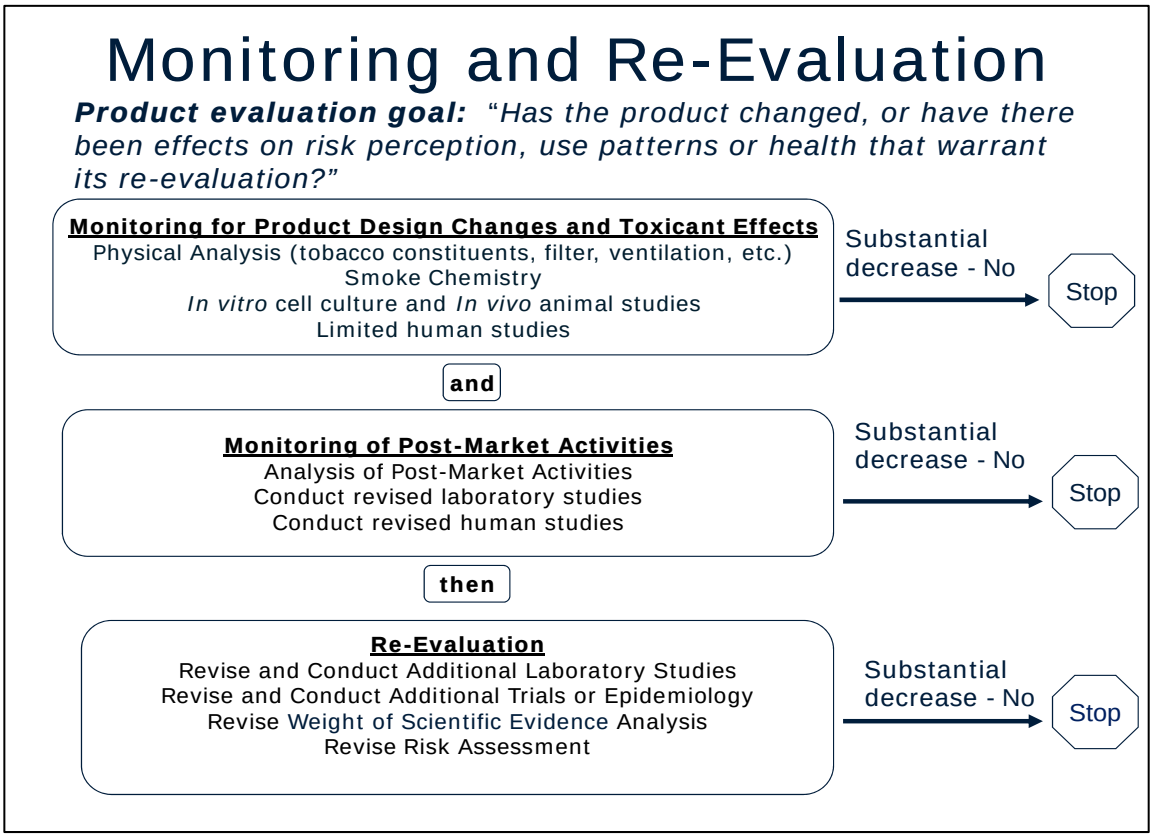



Figure 7. **Monitoring and Re-evaluation**

The monitoring and evaluation component includes three SEAs.

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## *Conflicts of Interest:*

The authors would like to declare the following conflicts of interest:

Peter G. Shields: Provides expert support and testimony in tobacco-related litigation on behalf of plaintiffs.

Greg Connolly: Serves as a consultant to the Food and Drug Administration and its Center for Tobacco Research as a member of the Tobacco Products Scientific Advisory Committee.

K. Michael Cummings: Salary support comes primarily from Roswell Park Cancer Institute and from research funding provided by the National Cancer Institute, the New York State Department of Health, the Robert Wood Johnson Foundation, the American Legacy Foundation, and the Flight Attendant Medical Research Foundation. He has also received payments as a paid expert witness for plaintiffs in litigation against the tobacco industry.

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Jack E. Henningfield: Serves as a consultant to the Food and Drug Administration and its Center for Tobacco Research as a member of the Tobacco Products Scientific Advisory Committee.

Matthew Myers: None. The Campaign for Tobacco-Free Kids has received donations from several pharmaceutical companies, including GlaxoSmith Kline and Pfizer. The Campaign has no other potential conflicts.

Richard J. O'Connor: Consultant to FDA, Tobacco Constituents Subcommittee, Tobacco Products Scientific Advisory Committee for the FDA.

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Mitchell Zeller: Employed by Pinney Associates who provides consulting services to GlaxoSmithKline Consumer Healthcare on issues related to treating tobacco dependence. Mr. Zeller is also a consultant to FDA's Center for Tobacco Products.

## *Author Contributions:*

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# REFERENCE LIST


(1) National Cancer Institute. Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. Smoking and Tobacco Control[Monograph 13]. 2002. Ref Type: Serial (Book,Monograph)

(2) Institute of Medicine, Committee to Assess the Science Base for Tobacco Harm Reduction, Board on Health Promotion and Disease Prevention. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: National Acadamy Press; 2001.

(3) Stratton K, Shetty P, Wallace R, Bondurant S, editors. Clearing the smoke: the science base for tobacco harm reduction--executive summary. *Tob Control.* 2001;10:189-195.

(4) Foulds J, Kozlowski L. Snus--what should the public-health response be? *Lancet.* 2007;369:1976-1978.

(5) Fagerstrom KO, Schildt EB. Should the European Union lift the ban on *snus*? Evidence from the Swedish experience. *Addiction.* 2003;98:1191-1195.

(6) Gartner CE, Hall WD, Chapman S, Freeman B. Should the health community promote smokeless tobacco (snus) as a harm reduction measure? *PLoS Med.* 2007;4:e185.

(7) Scientific Advisory Committee on Tobacco Product Regulation. *Statement of principles guiding the evalation of new or modified tobacco products*. Geneva, Switzerland: World Health Organization; 2002.

(8) Zeller M, Hatsukami D. The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tob Control.* 2009;18:324-332.

(9) Hatsukami D, Hecht S, Benowitz N, Oncken C, Rennard S. Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine & Tobacco Reseach.* 2006;8:169-191.

(10) Hatsukami DK, Hecht SS, Hennrikus DJ, Joseph AM, Pentel PR. Biomarkers of tobacco exposure or harm: application to clinical and epidemiological studies. 25-26 October 2001, Minneapolis, Minnesota. *Nicotine Tob Res.* 2003;5:387-396.

(11) Hatsukami DK, Benowitz NL, Rennard SI, Oncken C, Hecht SS. Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine Tob Res.* 2006;8:599-622.

(12) WHO Scientific Advisory Committee on Tobacco Product Regulation. Statement of Principles Guiding the Evaluation of New or Modified Tobacco Products. 2003. Geneva, Switzerland, World Health Organization.
Ref Type: Report

(13) WHO Study Group on Tobacco Product Regulation. Guiding principles for the development of tobacco product research and testing capacity and proposed protocols for the initiation of tobacco product testing . 2004. Geneva, Switzerland, World Health Organization.
Ref Type: Report

(14) Hatsukami DK, Giovino GA, Eissenberg T, Clark PI, Lawrence D, Leischow S. Methods to assess potential reduced exposure products. *Nicotine Tob Res.* 2005;7:827-844.

(15) Burns DM, Dybing E, Gray N et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. *Tob Control.* 2008;17:132-141.

(16) Marian C, O'Connor RJ, Djordjevic MV, Rees VW, Hatsukami DK, Shields PG. Reconciling human smoking behavior and machine smoking patterns: implications for understanding smoking behavior and the impact on laboratory studies. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3305-3320.

(17) Johnson MD, Schilz J, Djordjevic MV, Rice JR, Shields PG. Evaluation of in vitro assays for assessing the toxicity of cigarette smoke and smokeless tobacco. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3263-3304.

(18) Hatsukami DK, Hanson K, Briggs A et al. Clinical trials methods for evaluation of potential reduced exposure products. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3143-3195.

(19) Rees VW, Kreslake JM, O'Connor RJ et al. Methods used in internal industry clinical trials to assess tobacco risk reduction. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3196-3208.

(20) Rees VW, Kreslake JM, Cummings KM et al. Assessing consumer responses to potential reduced-exposure tobacco products: a review of tobacco industry and independent research methods. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3225-3240.

(21) Hanson K, O'Connor R, Hatsukami D. Measures for assessing subjective effects of potential reduced-exposure products. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3209-3224.

(22) Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3241-3262.

(23) Dart RC. Monitoring risk: post marketing surveillance and signal detection. *Drug Alcohol Depend.* 2009;105 Suppl 1:S26-S32.

(24) Dasgupta N, Schnoll SH. Signal detection in post-marketing surveillance for controlled substances. *Drug Alcohol Depend.* 2009;105 Suppl 1:S33-S41.

(25) Weed DL. Weight of evidence: a review of concept and methods. *Risk Anal.* 2005;25:1545-1557.

(26) Krimsky S. The weight of scientific evidence in policy and law. *Am J Public Health.* 2005;95 Suppl 1:S129-S136.

(27) PUblic Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. PHS publication No. 1103. 1964.
Ref Type: Report

(28) Hill AB. The environment and disease: association or causation. *Proc Royal Soc Med.* 1965;58:295-300.

(29) Parascandola M, Weed DL. Causation in epidemiology. *J Epidemiol Community Health.* 2001;55:905-912.

(30) International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. 83 ed. Lyon, France: IARC; 2004.

(31) International Agency for Research on Cancer. *Smokeless Tobacco and Some Tobacco-specific N-nitrosamines*. Geneva, Switzerland: World Health Organization; 2007.

(32) De Rosa CT, El-Masri HA, Pohl H, Cibulas W, Mumtaz MM. Implications of chemical mixtures in public health practice. *J Toxicol Environ Health B Crit Rev.* 2004;7:339-350.

(33) Boobis AR, Cohen SM, Dellarco V et al. IPCS framework for analyzing the relevance of a cancer mode of action for humans. *Crit Rev Toxicol.* 2006;36:781-792.

(34) Teuschler LK. Deciding which chemical mixtures risk assessment methods work best for what mixtures. *Toxicol Appl Pharmacol.* 2007;223:139-147.

(35) Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tob Control.* 2003;12:424-430.

(36) O'Connor RJ, Cummings KM, Rees VW et al. Surveillance methods for identifying, characterizing, and monitoring tobacco products: potential reduced exposure products as an example. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3334-3348.

(37) Pauly JL, O'Connor RJ, Paszkiewicz GM, Cummings KM, Djordjevic MV, Shields PG. Cigarette filter-based assays as proxies for toxicant exposure and smoking behavior--a literature review. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3321-3333.