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Providing a Science Base for the Evaluation of Tobacco Products

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Abstract

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Human Subjects Statement: This paper reports on the development of a conceptual framework for tobacco product regulation and did not involve any human subjects.

Objective—Evidence-based tobacco regulation requires a comprehensive scientific framework to guide the evaluation of new tobacco products and health-related claims made by product manufacturers.

Methods—The Tobacco Product Assessment Consortium (TobPRAC) employed an iterative process involving consortia investigators, consultants, a workshop of independent scientists and public health experts, and written reviews in order to develop a conceptual framework for evaluating tobacco products.

Results—The consortium developed a four-phased framework for the scientific evaluation of tobacco products. The four phases addressed by the framework are: (1) pre-market evaluation, (2) pre-claims evaluation, (3) post-market activities, and (4) monitoring and re-evaluation. For each phase, the framework proposes the use of validated testing procedures that will evaluate potential harms at both the individual and population level.

Conclusions—While the validation of methods for evaluating tobacco products is an ongoing and necessary process, the proposed framework need not wait for fully validated methods to be used in guiding tobacco product regulation today.

Keywords

Tobacco; FDA; Modified Risk Tobacco Products (MRTPs); Potential Reduced Exposure Products (PREPs); health claims; toxicology; chemistry; clinical trials; epidemiology; surveillance

Tobacco use remains by far the leading cause of preventable death in the United States, killing approximately 480,000 American each year. If current trends continue, 5.6 million U.S. children alive today will die prematurely from a tobacco-related disease.¹ With the enactment of the Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act), Congress provided the U.S. Food and Drug Administration (FDA) with an unprecedented opportunity to regulate the way in which tobacco products are designed, manufactured, sold, and marketed.² Although the FDA's authority is limited in some significant respects (for example, the FDA cannot ban an entire category of tobacco products), it has broad authority to adopt "product standards" relating to a product's characteristics or emissions, evaluate health-related claims made by manufacturers, require the disclosure of ingredients and health-related information, conduct pre-market review of new tobacco products, and limit the marketing and promotion of tobacco products. The goal of this paper is to present a conceptual scientific framework to help structure the evaluation of tobacco products in a way that can support 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. Although the U.S. regulatory structure is discussed in this article to provide context, the framework presented herein it is not specifically tied to the U.S. regulatory environment, and it does not address the legal standards or the full range of other considerations that a regulatory agency would take into account. The scientific recommendations presented here, which apply to both existing and new/modified products, are not based on any particular legal structure, and they are not intended as a substitute for the legal standards that the FDA or other regulatory agencies are authorized or required to

apply. In order to assist readers in understanding the framework presented in this paper, Table 1 provides definitions of key terms.

The established system of evaluating safety and efficacy that has been widely used by FDA for evaluating drugs and medical devices is not appropriate for tobacco products.³ Instead of applying the “safe and effective” standard used in other FDA regulatory contexts, the Tobacco Control Act sets forth a novel “public health standard.” This standard provides that the FDA may take regulatory action where “appropriate for the protection of the public health,” after “consider[ing] scientific evidence concerning ... the risks and benefits to the population as a whole, including users and nonusers of the tobacco product.”² The Act thereby presumes that tobacco products cannot be made entirely free of harm, but that the FDA can take effective action that will *reduce harm* to the population as a whole. According to the Congressional report that accompanied the Tobacco Control Act, the public health standard was “intended to be a flexible standard that focuses on the overall goal of reducing the number of individuals who die or are harmed by tobacco products.”⁴

In order to show that its regulations meet this public health standard, the FDA must have scientific evidence to support its actions. However, the Tobacco Control Act provides little specific guidance as to the form and/or amount of evidence necessary for the FDA to act, giving the FDA the same type of flexibility that it has in other regulatory areas to base its actions on the state of the science, expert input, projected public health implications, and other factors.⁵ Supported by expert guidance from the public health and scientific communities, it is left to the FDA in the first instance to interpret the public health standard in a health-protective manner aligned with Congress's intent. This will require a scientific framework that outlines the types and quality of evidence necessary for the FDA to make informed regulatory judgments. Undoubtedly, the application of the science-based standards adopted by the FDA will also be subjected to legal review through the courts.

This article focuses on the characteristics of a scientific framework specifically geared towards the evaluation of tobacco products. The urgent necessity for such a framework is demonstrated by the FDA's recent action to extend its regulatory authority to all tobacco products not currently subject to its oversight (with the possible exception of “premium” cigars).⁶ This will include Electronic Nicotine Delivery Systems (such as e-cigarettes) and other emerging products that may present a different or unknown risk of harm to individual users. Assuming that the FDA's proposed rule is finalized, the FDA will then be tasked with determining whether it is “appropriate for the protection of public health” to permit these new products to be marketed, whether claims of reduced exposure or reduced risk (referred to in the Tobacco Control Act as “Modified Risk Tobacco Product,” or MRTP, claims) can be substantiated by manufacturers, and what product standards, if any, should be applied to these products. Although the same questions will arise for conventional tobacco products (cigarettes, smokeless tobacco, cigars, etc.), novel products are likely to pose the most difficult and controversial regulatory questions because the products are new and less is known about their health risks. A scientific framework is needed in order to provide for consistent, transparent, and evidence-based regulatory decision-making as the FDA begins to confront these challenging questions.

Any framework for the regulation of tobacco products must consider three broad domains: exposure, individual risk, and population harm (including effects on former smokers, delayed quitting, youth initiation, and nonsmokers exposed to secondhand smoke). Public health considerations require that products be evaluated thoroughly in all three domains. Exposure reduction is a necessary component of risk reduction, but on its own exposure reduction may not translate into lower disease risk. For example, because tobacco products contain many known toxins and carcinogens, products containing lower levels of tobacco-specific nitrosamines may not be associated with lower disease risks. Although methods now exist to assess exposure reduction through biomarkers, there are no valid biomarkers that serve as proxies for tobacco-related disease.⁷⁻⁹ Likewise, individual risk reduction may not necessarily lead to a reduction in harm at the population level. Even if a tobacco product reduces harm for an individual user when used as a substitute for conventional cigarettes, it could potentially increase population-level harms if it encourages non-smokers to start using the product, reduces the number of people who quit tobacco use entirely, or induces former smokers to return to smoking. It is for this reason that the Tobacco Control Act requires the FDA to consider “the risks and benefits to the population as a whole”—and not simply individual users—when making regulatory decisions. In addition to these three broad domains, other key challenges include (1) the long latency of many tobacco-related diseases, which requires studies of long duration and decision-making based on incomplete data, (2) limitations in predicting how consumers are likely to respond to the availability of a new or modified tobacco product, and (3) understanding how usage patterns may translate into population risk.

The proposed framework assumes that various types of tobacco products can exist on a continuum of toxicant exposure, risk and harm (Figure 1). As scientific evidence suggesting—and then verifying—a reduced risk emerges, it would be possible for a product to move along the continuum towards harm reduction. Importantly, however, it cannot be assumed that this will be the case for any given product. Herein, we do not provide criteria to classify tobacco products on this continuum, and a classification scheme should not be inferred from Figure 1. 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.”¹⁰⁻¹⁶ The IOM termed such products “potential reduced exposure products” (PREPs), while the Tobacco Control Act refers to products that make health- or exposure-related claims as MRTPs. (This paper uses the term PREPs, rather than MRTPs, unless it is specifically referring to the FDA regulatory process.) All major tobacco companies, and some small ones, have marketed or currently market products that they have identified as PREPs—sometimes making explicit claims about reduced exposure or risk.

There are some examples of tobacco products, namely snus – a type of oral tobacco marketed in Sweden — that have been associated with lower tobacco-related mortality and morbidity at the population level (compared with other types of tobacco products).¹⁷ However, it is unclear whether the Swedish experience with snus as a substitute for conventional cigarettes can be replicated in the United States, where early evidence suggests that smokers are unwilling to substitute snus or other forms of oral tobacco for conventional cigarettes.¹⁸⁻¹⁹ However, there are also many examples of tobacco products marketed with

reduced risk claims that have been shown not to be associated with lower tobacco related mortality. Examples of these so-called reduced harm products include filtered and low tar or “light” cigarettes (examples of PREPs are available at www.tobaccoproducts.org).

The public health dilemma regarding these products is that exposure reduction 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 challenging, because it is possible that the marketing of PREPs could promote continued tobacco use by delaying quitting, promoting dual use of tobacco products, inducing former tobacco users to resume use, and enticing non-tobacco users to initiate tobacco use, perhaps in response to lowered perceptions of risk.^{10,16,20}

A scientific framework for tobacco regulation must also be constructed with the tobacco industry's history in mind.¹ In her landmark 2006 decision, Judge Gladys Kessler found that for nearly half a century the major tobacco companies had “vigorously—and falsely—denied the existence of any adverse health effects from smoking [and] mounted a coordinated, well-financed, sophisticated public relations campaign to attack and distort the scientific evidence demonstrating the relationship between smoking and disease.”²¹ Despite their own knowledge of the link between smoking and disease, the tobacco companies continued to argue that it was an “open question.”²¹ At the same time, they marketed a succession of products intended to alleviate consumers' health concerns and dissuade them from quitting entirely. Examples of products marketed with implicit or explicit health claims included “light” and “ultralight” cigarettes with ventilated filters, cigarettes with filters designed to remove selected toxicants, and “low tar” cigarettes. Despite manufacturers' claims, these products did not decrease risk and instead may have increased risks while dissuading millions of smokers from quitting.^{7,21,22}

Given the history of the tobacco industry's misconduct, regulatory agencies must be cautious in their evaluation of the industry's assertions, particularly claims of reduced risk. While some emerging products may have the potential to lower health risks, the existing methods for assessing reduced-risk claims have limitations and rest mostly on the unproven assumption that reduced toxicant exposure necessarily reduces disease risk.¹ The claim that “less ought to be better” must be evaluated and independently verified before it is used as the basis for regulatory action. Although the tobacco industry has proposed relying heavily on laboratory studies (ie, chemistry and animal toxicology) to assess reduced-risk claims,²³ human studies are required to directly assess the impact of design changes on exposure, and ultimately on disease risk. Human exposure studies are therefore essential in tobacco product evaluation for regulatory purposes. Moreover, even when human studies suggest reduced risk at the individual level, population-level impacts must be modeled and analyzed as well before reaching any regulatory decisions.

Previous Recommendations for Tobacco Product Assessment

The TobPRAC framework presented below is the first *comprehensive* framework for the scientific evaluation of tobacco products. Previously developed recommendations for the review of tobacco products have focused almost exclusively on the review of PREPs—

products that may reduce toxicant exposure or risk—and have not sought to develop a broader evaluation process that would encompass products that do not make health-related claims. In order to demonstrate the need for a new scientific framework for tobacco product evaluation, this section briefly reviews prior recommendations from both the IOM and the World Health Organization (WHO), as well as those from the tobacco industry.

In *Clearing the Smoke: Assessing the Science Base For Tobacco Harm Reduction*, the IOM considered the feasibility of harm reduction through continued tobacco use.¹⁵⁻¹⁶ The IOM's report concluded that although no PREPs had been sufficiently evaluated to conclude that one or another could decrease risk, it was possible that validated biomarkers could be used to predict reduced health risks. The IOM determined that regulation of all tobacco products was needed to implement a strategy for harm reduction, but it did not attempt to provide a framework for comprehensively assessing tobacco products. Its report stopped short of identifying studies to be incorporated into a product assessment or indicating 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.²⁴ It recommended 10 principles and conclusions regarding the types and quality of evidence needed to examine new tobacco products, including a call for analysis of their physical chemical characteristics, constituents, emissions, 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 next 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.”²⁵ The document also distinguished research activities from testing activities: the former relating to better understanding the nature of tobacco products and their use, and the latter relating to repeated examination and evaluation according to standardized methods to assess product performance. A point of note is TobReg's conclusion that research and testing should be interactive and iterative and should include analysis of a product's physical characteristics, chemistry, toxicology, and behavioral use patterns.

In 2004, with funding by the National Cancer Institute, the Centers for Disease Control and Prevention, 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 colleagues 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.⁸ 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.⁸

The IOM more recently released a report on *Scientific Standards for Studies on Modified Risk Tobacco Products* that built on the 2001 IOM report and developed some specific recommendations regarding the scientific studies needed to inform MRTP decisions by the FDA.²⁶ The IOM's recommendations overlap somewhat with those presented below, and in particular with those discussed in the second phase of the second phase of the TobPRAC framework. However, there are three important distinctions between the IOM's report and the TobPRAC framework: 1) The IOM report is specifically focused on FDA regulation under the Tobacco Control Act, whereas the TobPRAC framework is not linked to any specific regulatory system; 2) the IOM report considers only on the review of *Modified Risk Tobacco Products* and, unlike the TobPRAC framework, does not discuss products that do not make any health- or exposure-related claims; and 3) the TobPRAC framework is a broader, conceptual document intended to guide the overall process of product review, while the IOM report is a more technical document that examines specific *methods* for studies conducted in the MRTP context.

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 (PRRTPs).”²³ 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 *Exposure Assessment in the Evaluation of Potential Reduced Risk Tobacco Products* (http://www.lsro.org/articles/rrrvw_report_040308.html). LSRO's proposed 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. It 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 minimum. Potentially incongruent with a harm reduction process, it 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 in LSRO's reports 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 assess a health claim of a PREP.

The British-American Tobacco Company (BATCO) also developed an approach to PREP evaluations.²⁷ 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.”²⁷ Unlike LSRO, the BATCO group did not find significant utility in animal studies. It should be noted that the BATCO framework, as presented, did not address important issues such as downstream effects (eg, re-uptake, initiation, and reduced cessation) and gave little importance to the role of consumer reactions to and perceptions of PREPs. Neither the LSRO nor BATCO approaches formally included evaluation of products already introduced into the market.

Importantly, these industry-sponsored frameworks focus almost exclusively on exposure reduction claims surrounding the introduction of PREPs, and do not offer comprehensive approaches for evaluating tobacco products. For example, the tobacco industry-sponsored frameworks fail to address how consumers may perceive and use these products, and how the availability of these new products might ultimately impact overall tobacco use patterns and population health. Thus, they do not adequately consider new or modified product usage patterns within the context of how all available tobacco products are used, which is an essential requirement for evaluating the population-level risk of PREPs.²⁶

In response to the need for a systematic approach to the assessment of tobacco products, the Tobacco Product Assessment Consortium (TobPRAC)—consisting of investigators from Georgetown University Medical Center, the University of Minnesota, Roswell Park Cancer Institute, and Harvard School of Public Health—was established under a contract from the National Cancer Institute. The aim of the project was to develop a framework for the comprehensive evaluation of tobacco products, and to identify research and infrastructure gaps critical to future regulatory science needs.

Methods

Through a two-year iterative process, experts representing diverse scientific disciplines considered various approaches to comprehensive product evaluation. Two central principles were used to guide the approach: (1) that the introduction or modification of tobacco products must not increase harm (eg, by elevating disease risk, increasing initiation, or delaying smoking cessation) and instead must reduce harm at the population level, and (2) that tobacco manufacturers' health-related or exposure-related claims about tobacco products must be verifiable and lead to a reduction in harm at the population level. After a draft framework was developed by subset of TobPRAC members, independent scientists and public health experts evaluated the proposed assessment framework during a two-day workshop. Following revisions based upon the recommendations, additional written comments were solicited from other experts and a final consensus document was developed. These deliberations were conducted to help guide regulation of tobacco products by government entities such as the FDA. However, this process was conducted independent of any specific regulatory process or entity.

The following objectives were established to guide development of the tobacco product assessment framework:

1. Provide a means for scientifically evaluating tobacco products, including existing combustible and smokeless products as well as potentially reduced-risk products.
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 new tobacco products;
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 process to categorize and prioritize research gaps.

The follow section presents the framework developed by TobPRAC and also discusses the relationship between the framework and FDA tobacco regulatory actions to date.

Results

Figure 2 provides an overview of the framework for tobacco product assessment. The framework consists of four phases, each of which includes specific assessment strategies that can provide an empirical basis for demonstrating the risk a given tobacco product. The four phases are: (1) pre-market evaluation; (2) pre-claims evaluation; (3) post-market activities; and (4) monitoring and re-evaluation. The second phase, pre-claims evaluation, is relevant only if health-related or reduced exposure claims are anticipated. (A more detailed explanation of the framework is available at <http://cph.osu.edu/certs/external-links>.)

Each phase of the process has a Product Evaluation Goal (PEG) that defines the core purpose of the phase, or the key research question to be addressed (Table 2). Achieving the goal for each phase requires several “Substantial Evaluation Assessments” (SEAs). These SEAs identify specific types of data to be collected and analyzed. All SEAs within a particular phase are required if one is to conclude that the goal for that phase has been met. The framework requires consideration of the heterogeneity among individuals and population subgroups (eg, different use, perception, and harm by race, sex, age, smoking history, metabolic capacity, genetics, and health status). This is particularly critical if a new product appeals to or is marketed specifically towards a population subgroup.

The four phases of the framework can be summarized as follows:

1. Pre-market evaluation

This first phase occurs before a new product is introduced onto the market, and it is applied to all new products, whether or not they make exposure- or health-related claims. The goal for this phase 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?*”ⁱ This is evaluated by SEAs that include: (1) assessment of the tobacco product design, physical performance, characteristics, and contents; (2) laboratory chemical and toxicological analysis (*in vitro* and *in vivo*); and (3) human testing

that allows for some level of confidence that the laboratory testing mimics human use. Although all SEAs are required to inform the PEG, an initial assessment of laboratory study results would be required before testing in human subjects. If laboratory results identified any worsening of overall toxicant exposure in comparison to the reference products, human testing would not be required at this point since product marketing would be prohibited. If the process continued to human testing, the data collected on human use patterns would then inform the operational parameters of additional laboratory testing. For example, smoking machine puff profiles could be recalibrated to better mimic actual smoking behavior. The scope and amount of human testing would depend on the novelty of the product. A battery of chemical and toxicological tests would be employed to ensure the safety of the test subjects; human testing would be halted if increases in overall toxicant exposure (in comparison to the reference product) were identified.

Human studies are the *sine qua non* for understanding tobacco-related disease risk, including addiction risk, at the individual level. Pre-clinical laboratory studies (eg, smoke constituent analyses, and *in vitro* and *in vivo* toxicology assessments) are useful for screening the potential impact of product design changes and ensuring that there are no obvious unintended consequences. However, no new product should be permitted to enter the market without at least some human testing, because only such studies can directly assess the impact of the product's use. Even human studies, though, have limitations. Most notably, because of the long latency period of many of the illnesses caused by tobacco use, the risk profile of a new tobacco product cannot be fully known for decades. In principle it would be possible to use intermediate biomarkers of disease risk as proxy measures to predict risk reduction. As illustrated by recent studies, a validated biomarker—one 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 the future risk of a disease.^{9,28} However, even with validated biomarkers of disease risk, the population-level impact of marketing a lower risk tobacco product would still need to be assessed.

With respect to addiction, abuse liability and comparisons of addiction risk across products can be evaluated in human laboratory studies according to standardized methods. For example, guidance from the FDA Center for Drug Evaluation and Research (CDER) outlines methods that have been used to assess many nicotine products and other drugs across various routes of administration.²⁹ As strikingly illustrated by the rapid proliferation and evolution of Electronic Nicotine Delivery Systems, product design features are likely important determinants of use and addiction risk. Such design features can be evaluated by extension of the methods described by CDER in its guidance for assessing abuse deterrence (and, conversely, abuse and addiction risk) in diverse opioid formulations.³⁰

Completion of all the SEAs would provide regulators with essential information needed to compare the new product to conventional or reference products. Nonetheless, given the

ⁱ*Conventional* products are those most commonly sold in the marketplace. For example, if a new cigarette were being analyzed, it would be compared to a “typical” cigarette currently being sold (eg, a Marlboro cigarette). *Reference* products are standardized products used in laboratory studies (eg, the Kentucky reference research cigarette). Both conventional and reference products should be used in this phase in order to compare new products to those currently on the market while also controlling for and assessing changes in conventional products over time.

latency period of diseases, the various ways a product could be used by consumers (eg, in combination with other products), and the inability to study population-level effects before a product is introduced, regulatory decisions will inevitably be made in the context of considerable uncertainty. The decisions regulators make in such circumstances will depend on the legal framework being applied and policy judgments regarding the appropriate response to potential risks and benefits. For example, a regulatory body might use the premarket evaluation phase to only allow products on the market that are *substantially likely to reduce* exposure, risk, and population harm, relative to conventional products currently on the market. Alternatively, a regulatory entity could allow the sale of products that are *likely to be no more harmful* than products already on the market (a much less restrictive standard). This framework takes no position on the appropriate standard to be applied.

In the U.S., the Tobacco Control Act's public health standard is subject to a variety of potential interpretations. To date, the FDA has not yet ruled on any Premarket Tobacco Product Applications (PMTAs), and therefore it has not had to explain how it will interpret the public health standard in this context. The FDA has, however, issued non-binding draft guidance to the tobacco industry describing the types of studies that should be submitted with a PMTA.³¹ In line with the recommendations of this framework, the FDA's guidance recommends the submission of product chemistry studies, nonclinical (*in vitro* and *in vivo*) evaluations of toxicity and carcinogenicity, and adult human studies examining the effects on human health and behavior (including "tobacco use topography, toxicant exposure and biological effect, abuse potential, and consumer perception"). Although the draft guidance calls for "measures to ensure the reliability and validity" of studies, such as use of a pre-specified data analysis plan, it does not require oversight by independent third parties, as recommended by the IOM.²⁶

2. Pre-Claims Evaluation

This second phase occurs only when there are proposed health-related or reduced exposure claims. The goal for this phase 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 potentially reduced-risk products (PREPs)?*"ⁱⁱ. In other words, is there a scientific basis supporting the proposed claim in terms of reduced toxicant exposure, reduced individual risk, *and* reduced population risk? It is assumed that any manufacturers' claims would be evaluated for a potential effect on disease reduction, even if the proposed claim refers only to levels of exposure. The SEAs for this phase include (1) human clinical trials of sufficient scope, quality, size, and duration; (2) epidemiological studies of use patterns and effects of use of products already on the market; (3) health claims and product messaging evaluation; (4) weight of scientific evidence review; and (5) risk assessment.

ⁱⁱThis Pre-Claims Evaluation would require comparison of the product under study with conventional products on the market, and/or other potentially reduced-risk products on the market, depending on the nature of the claim. For example, a product that claimed "50% fewer carcinogens than typical cigarettes" would be compared to conventional and reference cigarettes. A product that claimed "50% fewer carcinogens than [PRODUCT X]" would be compared to Product X.

Only human data can substantiate a human health claim. Therefore, randomized clinical trials (eg, switching users of conventional products to the test product) would be necessary to support any claim of reduced risk. Exposure reduction would be validated via a battery of biomarkers that are chemically specific, and complex biomarkers that are not chemically specific but are suitable for screening for unexpected changes in toxicant yields. As above, any increase in toxicant exposure would lead to an end to testing and rejection of the proposed claim. If the product is currently on the market, epidemiological studies would be required to evaluate the product's use and its impact on various populations (including vulnerable populations). If the product is not currently on the market, the lack of epidemiological data may make evaluation of the proposed claim impossible, and therefore some period of time on the marketplace without any claims may be required as a first step before any claims can be reviewed.

In addition, studies evaluating consumer perceptions and consumer use intentions are necessary to inform this phase. As noted by the IOM, "Of particular importance are adolescents' perceptions of the risks and benefits of using the product, and whether they intend to initiate tobacco use with the [PREP] rather than a traditional tobacco product because they believe the latter is a 'safe' alternative."²⁶ In addition to explicit claims, product characteristics such as packaging color, packaging design, and the presence of a filter have been shown to influence consumer beliefs about health risks.³²⁻³⁶ Thus, consumer perception studies should examine not only consumer responses to the proposed health claims, but also the potential effects of the product's marketing, packaging, and design characteristics.

Data from the pre-market evaluation and from these clinical, epidemiological, and consumer perception studies would then be integrated into a weight of scientific evidence review that would make a qualitative decision regarding the validity of the proposed claim (eg, "will," "probably will," "possibly will," or "will not" reduce risk). Next, a quantitative risk assessment would be conducted to model the likely effects (positive or negative) on both individual and public health, again with consideration given to the impact on susceptible populations. The risk assessment would use mathematical modeling to project the likely effects on youth initiation, smoking cessation rates, and long term quitting, among other factors. Notably, new methodologies need to be developed for the weight of scientific evidence review and risk assessment, which are unprecedented in the context of tobacco regulation and will necessarily differ from those conducted by other FDA centers and other regulatory agencies such as the Environmental Protection Agency (EPA).

As with the pre-market evaluation, whether a regulatory agency decides to authorize a reduced-risk claim will depend on the legal standard to be applied and other regulatory considerations. For example, using a weight of scientific evidence type of analysis, a regulatory entity might permit claims only for those products that "will" reduce risk, or it could take a more permissive stance and permit claims for products that "probably will" reduce risk in comparison to conventional products on the market (or to other reduced-risk products, depending on the nature of the claim). Additionally, it could factor in the risk assessment and only allow claims for products that are likely to reduce risk by some

specified amount. A regulatory entity might also permit claims while imposing limits on the nature or extent of marketing permitted.

3. Post-market activities

The third phase, applicable to all products that are permitted to reach the market, involves the use of population-wide surveillance, epidemiology, and consumer use studies to assess health-related outcomes. The goal for this phase is, “*How does the product affect consumer use (eg, increase initiation, increase intensity, or reduce cessation), biomarkers, and health outcomes on an individual and population basis?*” When health claims are authorized for product marketing (in phase 2), the post-market activities phase will also be used to evaluate the accuracy and impact of those claims. The SEAs for this phase include (1) population-wide surveillance; (2) epidemiological studies (including cross-sectional and cohort studies), and (3) intervention studies for disease outcomes (if claims were made about specific disease outcomes).

Post-market activities are particularly important for identifying unintended consequences and unexpected disease outcomes associated with specific products. This work, however, is complicated by the fact that product design may change and by the long latency period associated with some diseases. Accordingly, novel and flexible surveillance methodologies will need to be developed. In addition, all three types of studies conducted in this phase must be robust and sensitive enough to detect disproportionate impacts on high-risk populations.

The legal standard (and, accordingly, the degree of scientific evidence required) to withdraw a product from the market will vary from country to country. But it should be noted that in both practical and legal terms, withdrawing a product from the market is likely to be much more difficult than denying pre-market authorization. Once a product has been widely distributed, it is likely to have loyal users who will advocate for its continued availability, and the manufacturer can claim that it has invested a considerable amount of money in product production, sales, marketing, etc., in reliance on the regulatory agency's prior decision to allow the product to be sold. Under the Tobacco Control Act, pre-market approval of a product can be withdrawn by the FDA if it determines that the “the continued marketing of such tobacco product is no longer appropriate for the protection of the public health,” but unlike in the pre-market review phase, the burden of proof lies with the FDA, not the manufacturer.² Moreover, the manufacturer is provided with expanded legal protections, such as a right to a hearing and an administrative appeal of an adverse decision. Legal commentators have noted that “[s]imilar actions with respect to other FDA-regulated product categories suggest that [seeking to withdraw a product from the market] would be time and resource intensive,” and that “[a] similar provision in the Medical Device Amendments has rarely been used in the many years since it took effect.”³⁷ Although other regulatory systems may operate somewhat differently, this example shows the importance of making sound, evidence-based decisions in the pre-market approval phase and not relying predominantly on post-market review.

4. Monitoring and re-evaluation

Monitoring and re-evaluation is defined as a distinct phase in the framework in order to emphasize the importance of ongoing review even after the first three phases have been completed. The goal for this phase is, “*Has the product changed, or have there been effects on risk perception, use patterns, or health that warrant its re-evaluation?*” Since manufacturers could modify existing products on the market in ways that could alter their exposure profile and consumer usage patterns, post-market activities are needed to routinely test all tobacco products to ensure they are not altered in ways that could influence disease risk in ways that are not predicted. The three SEAs for this phase are (1) monitoring for product design changes and toxicant effects; (2) monitoring of post-market activities (eg, product marketing and use patterns); and (3) re-evaluation. If, for example, use surveys show significant and unexpected shifts in consumption patterns (eg, increased use by minors), it may be necessary to revise the previously conducted weight of scientific evidence review and risk assessment. This may lead to a regulatory decision to withdraw a product from the market or revoke authorization for a health-related claim. Specific criteria for triggering a re-evaluation will need to be developed.

Under the Tobacco Control Act's regulatory scheme, any modification to a tobacco product's design requires the manufacturer to submit either a new product application (PMTA) or a “substantial equivalence” report (discussed further below).² The monitoring and re-evaluation phase can serve as a check to ensure that tobacco manufacturers are complying with these obligations and not secretly modifying the composition of tobacco products, as they have done in the past.¹

Notably, the Tobacco Control Act does not contain any provision that would allow the FDA to withdraw a “grandfathered” tobacco product (a product commercially marketed as of February 15, 2007 that has not been changed) from the marketplace. However, grandfathered products are subject to generally applicable tobacco product standards and marketing restrictions. The monitoring and re-evaluation phase could therefore be used to identify problematic product characteristics and marketing practices that could be addressed through the adoption of such regulations. Product manufacturers should remain under a continuing obligation to conduct and disclose post-market surveillance, notify the regulatory entity of any design changes to their products, and any immediately report any newly discovered adverse health effects.

Discussion

The research objectives and assessment strategies included in the proposed conceptual framework are focused on establishing that tobacco products introduced into the market reduce harm, and that health-related claims made by product manufacturers are verifiable. The intent in developing this framework was for it to be applicable to all forms of tobacco products, including those already on the market. 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 be applicable in any jurisdiction and to provide a logical and 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 some potential pitfalls, it reflects the need to ensure adequate evaluation of a complex public health problem where prior history dictates caution.

The framework has four components, each composed of a PEG and SEAs that allow for a conclusion as to whether the product under review is significantly different from a conventional or reference product—in terms of product characteristics, toxicology, and projected public health effects. The Pre-Claims Evaluation is a separate process due to its complexity and potential impact of health-related claims on human use and behavior. This phase requires human studies of sufficient scope, quality, size, and duration to inform 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, but is not used by some other government entities such as the EPA. Although these tools are used in other contexts, many aspects of a weight of scientific evidence review and risk assessment will be unprecedented as applied to tobacco (which is both uniquely dangerous and strongly addictive).

A considerable amount of research is needed to update and further validate methods and approaches for testing tobacco products as described in the framework. Depending on the context, it may not yet be possible to fully implement the framework, because it calls for some research methods and infrastructure needs that do yet exist or are not yet validated. Notably, TobPRAC has previously published a series of papers that provide a critical review of many aspects of tobacco research and identify key research gaps.^{21,38-45} For example, the scientific certainty of decisions will be improved as more knowledge is developed for: (1) better characterizing how toxicant yields and effects in the laboratory relate to the broad range of human use; (2) identifying a battery of validated biomarkers for disease risk; (3) evaluating of the impact of complex chemical exposures on human health, including additive, synergistic, and antagonistic effects; (4) understanding the relationship of 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 assessments in the context of inherent uncertainties. In the U.S., the FDA and National Institutes of Health (NIH) have already made a significant investment in regulatory research infrastructure, including the establishment of fourteen Tobacco Centers of Regulatory Science (TCORS) that can help address the research needs identified in this framework.⁴⁶

Despite ongoing research needs, this framework should be immediately useful in helping to inform the regulation of tobacco products. It is left to the regulators in each jurisdiction, after consideration of the applicable legal standards, to determine the criteria to be used in evaluating whether the SEAs have been met. Given the tobacco industry's history of public deception, it is important that such decisions be made independent of industry influence, as called for in Article 5.3 of the Framework Convention on Tobacco Control.⁴⁷ While this framework anticipates that manufacturers will be primarily responsible for conducting and funding many of the studies required (with full disclosure of study design, execution, and data), independent assessments not funded by the tobacco industry are necessary to verify

key industry data. Regulatory agencies should create panels of experts—unaffiliated with and not funded by the industry—that can assist in the scientific review process. (Under the Tobacco Control Act, the FDA will receive input on MRTTP applications from the Tobacco Products Scientific Advisory Committee, which consists of independent scientists but also includes non-voting industry representatives.²)

Some may view this framework as overly restrictive, in that it calls for clinical studies, epidemiological analysis, laboratory studies, chemical analyses, population surveillance, and other activities that may be difficult and expensive for manufacturers to conduct. In addition, specific aspects of the framework may be challenging for some manufacturers to satisfy, particularly given the need for large enrollments and studies of sufficient duration in the context of diseases with long latency. These requirements may have the undesired effect of stifling innovation or barring products from the market (at least for some time period) that might ultimately prove beneficial to public health, although clearly the major tobacco manufacturers have the resources to conduct such studies. Importantly, given the history of the tobacco industry, where the tobacco industry deceptively promoted products as lower harm, a regulatory agency's primary focus should be on ensuring that new products being introduced into the market *reduce* harm at the population level and that any health-related claims can be independently and conclusively verified. Given the scope of tobacco use and of tobacco-related death and disease, a mistaken regulatory decision that authorized the sale of a product that *increased* harms could have severe adverse implications for public health (and potentially for the regulatory agency's future credibility). Thus, the requirement for a significant amount of resources in order to establish the validity of health claims, for example, should not be considered overly burdensome given the historical context and the potential public health implications at stake.

Since the time that the TobPRAC group was convened to develop this framework, the FDA has begun the process of reviewing applications from the tobacco industry to permit the marketing of new products. Although the FDA's draft guidance on PMTAs follows this proposed framework in many respects, we note with concern that nearly all new product submissions from the tobacco industry have used the alternative, and less restrictive, “substantial equivalence” (SE) pathway. Under SE review, a tobacco manufacturer must only demonstrate that a new tobacco product “has the same characteristics” or “does not raise different questions of public health” when compared to a predicate product that was commercially marketed as of February 15, 2007.² Because products for which an SE report was filed by March 22, 2011 may be sold without prior authorization until such time as the FDA evaluates the manufacturer's report, tobacco manufacturers filed many SE applications shortly prior to that date (3,491 SE applications were filed in March 2011 alone).⁴⁸ As of September 2014, the FDA had received nearly 4,500 applications for SE review (or exemption from SE review), compared to only 4 PMTA applications (all of which FDA refused to file due to missing information).⁴⁸ This raises significant concerns that the tobacco industry may be seeking to evade PMTA review by inappropriately seeking to categorize products as “substantially equivalent” that are more accurately viewed as new tobacco products. If the SE process is being abused in this manner, it would compromise the ability of the FDA to implement the type of scientific framework described above.

Challenges and Limitations

Tobacco use and its effects on human health are complex, and that is reflected in the complexity of the conceptual framework proposed herein. However, the scope of the framework, including its many components and research gaps, should not deter regulators from undertaking a tobacco assessment process that is fully comprehensive. While the validation of methods for evaluating tobacco products is an ongoing and necessary process, the proposed commonsense framework need not wait for fully validated methods to be used in guiding tobacco product regulation today. Indeed, as described above, withdrawing a product from the market present far greater challenges than denying premarket authorization.

Nonetheless, there are significant potential pitfalls if regulators act prematurely and make mistaken judgments based on incomplete information. These could include a worsening of public health from tobacco-related disease due to widespread use of a product that is no different or perhaps more harmful 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. Other potential pitfalls relate to the tobacco industry and the creation of disincentives for real change because a SEA inadvertently focuses research on the wrong studies, results in misleading findings, or uses the wrong evaluation criteria. Additionally, if a SEA is seen as impossible or difficult to accomplish, it might discourage innovation.

There are also broader considerations, such as the ethical issues involved in balancing the risk of consumer misperception and the inappropriate use of a new tobacco product against the risks of withholding information from consumers (which could potentially remove an incentive to switch away from a more harmful product). A final risk 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.

Implications for Tobacco Regulatory Science

In the U.S. and worldwide, there are unprecedented opportunities for 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 and engage in the development of needed assessment tools and methodologies. The comprehensive framework for tobacco product assessment outlined here applies validated test methods to examine both individual and population-level risk, and provides an urgently needed foundation for tobacco product regulation.

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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.

Micah Berman: Has served as advisor and consultant to the Food and Drug Administration Center for Tobacco Products.

Gregory N. Connolly: Serves as a consultant to the Food and Drug Administration and its Center for Tobacco Products and was a past-member of the Tobacco Products Scientific Advisory Committee.

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Jack E. Henningfield: Vice President for Research, Health Policy & Abuse Liability at PinneyAssociates. Through PinneyAssociates, he has consulted to GlaxoSmithKline Consumer Healthcare on smoking cessation, NJOY on electronic cigarettes, and testified in litigation against the tobacco industry. He advises pharmaceutical developers on the evaluation and regulation of medications with respect to their potential for abuse and addiction. He shares ownership in a novel nicotine medication an option for which has been sold to Niconovum USA, and consults on tobacco harm minimization (including nicotine replacement therapy and digital vapor products) to Niconovum USA, RJ Reynolds Vapor Company, and RAI Services Company, which are all subsidiaries of Reynolds American Inc.

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Jerry M. Rice: None

The Continuum of Tobacco Products and Harm Reduction

Figure 1.

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 proposed Conceptual Framework, a product might be considered a reduced harm product. This figure is not meant to imply a classification scheme.

TobPRAC's Conceptual Framework

Figure 2.

The Conceptual Framework proposed in this report comprises four components. Each component includes an overall goal and a list of the specific types of data needed to evaluate whether the goal for that phase has been met. Additional detail and figures for each component, contexts and pitfalls can be found in the full report as [supplemental material](#).

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 (eg, through advertising, labeling, press releases, public statements, scientific publications and presentations, or messaging). Claims can be written, oral, or visual (eg, product packaging).
Conventional products	The most popular products on the market in a similar class (ie, 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 (eg, 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 through 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 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 (ie, physical analysis and <i>in vitro</i> and <i>in vivo</i> animal studies).
Modified Risk Tobacco Product (MRTP)	A tobacco product that potentially reduces a person's exposure to tobacco toxicants and risk of disease as compared with conventional products. There is a specific definition within the FDA legislation, and is tied to health claims. (Non-tobacco MRTPs 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 (eg, race, sex, age, co-morbidities, tobacco preference, tobacco use history, and genetic susceptibilities).
Product Evaluation Goal (PEG)	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.”
Potential Reduction Exposure Product	Includes MRTPs, and is conceptually similar, but is a broader term to include tobacco products that may reduce exposure generally, independent of any claims made.
Reverse dose-response relationship	Reduction in exposure must be 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 (SEA)	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 and substantial changes in exposure, risk, or harm reduction (eg, 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 (eg, 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 and its marketing 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 potentially reduced-risk products?
Post-Market Activities	Does the product adversely affect consumer use, biomarkers and health outcomes on an individual and population basis? For products 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?