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Review

Tobacco and Nicotine Product Testing

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Abstract

Introduction: Tobacco product testing is a critical component of the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which grants the Food and Drug Administration the authority to regulate tobacco products. The availability of methods and measures that can provide accurate data on the relative health risks across types of tobacco products, brands, and subbrands of tobacco products, on the validity of any health claims associated with a product, and on how consumers perceive information on products, toxicity or risks is crucial for making decisions on the product's potential impact on public health. These tools are also necessary for making assessments of the impact of new indications for medicinal products (other than cessation) but more importantly of tobacco products that may in the future be marketed as cessation tools.

Objective: To identify research opportunities to develop empirically based and comprehensive methods and measures for testing tobacco and other nicotine-containing products so that the best science is available when decisions are made about products or policies.

Methods: Literature was reviewed to address sections of the FSPTCA relevant to tobacco product evaluation; research questions were generated and then reviewed by a committee of research experts.

Results: A research agenda was developed for tobacco product evaluation in the general areas of toxicity and health risks, abuse liability, consumer perception, and population effects.

Conclusion: A cohesive, systematic, and comprehensive assessment of tobacco products is important and will require building consensus and addressing some crucial research questions.

Introduction

One of the most important tools granted to the Food and Drug Administration (FDA) under the Family Smoking Prevention and Tobacco Control Act (FSPTCA) is the ability to require appropriate testing and evaluation of tobacco products. Over time, this testing will enable the agency to enact product standards to control and reduce the delivery of toxic compounds in tobacco and tobacco smoke. It will also serve as the cornerstone for evaluating requests submitted by manufacturers to market new products or make product-specific health claims. Appropriate testing and evaluation of new tobacco products and claims on a premarket basis will help ensure that the overall objectives of the legislation are met, namely that a regulatory program is established that will protect public health.

The legislation also specifies that the FDA considers new ways to use medications or innovative drugs or products that would reduce the health burden from tobacco use. Testing indications for medications other than for cessation or testing products that are associated with reducing harm or tobacco use will also require evaluation tools so that no undue population harm occurs.

An important component of product testing concerns the consumer's perception of relative risks associated with the product. The FSPTCA requires that harmful and potentially harmful constituents and the quantities of these constituents across tobacco product brands are made available to the public. The availability of this information has implications for tobacco product standards, modified risk products, and even medicinal nicotine products. Research will be needed to determine how this information should be presented to the public so that consumers are not misled.

Methods and measures are the scientific building blocks of product testing (Hatsukami et al., 2005; Warner, 2009). Where they do not yet exist, they need to be devised and validated. Once validated, these tools can be used by government, researchers, and manufacturers as part of a comprehensive product testing regulatory program similar to those used by federal regulatory agencies to evaluate other consumer products.

The goal of this article is to identify research needs and describe a research agenda to guide future science-based evaluation

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of tobacco products and other nicotine delivery systems. Four primary tobacco product areas covered in this article: (a) modified risk products, (b) drug or other products used to treat tobacco dependence (c) tobacco product standards, and (d) consumer perception of levels of harmful and potentially harmful constituents across different types and brands of tobacco. For each of these areas, the following information are provided: (a) description of the law, (b) brief history of regulation, (c) brief description of what is known about the area, and (d) research opportunities. The process and methods used to produce the "white papers" that comprise this themed issue on the science to inform FDA regulatory actions are described in the article written by Leischow, Zeller, and Backinger (2011).

Framework to Assess Population Impact

Tobacco product evaluation involves assessment of multiple factors in order to determine the product's effect on public health or population harm. As described in the Institute of Medicine report, *Clearing the Smoke*, population harm (morbidity and mortality associated with tobacco use) is a function of toxicity of the product (per use), the intensity of its use (per user), and the prevalence of use (Stratton, Shetty, Wallace, & Bondurant, 2001). Figure 1 shows an example of various factors that are associated with determining population harm (modified from Hatsukami & Parascandola, 2010). Toxicity is associated with the levels of toxic constituents and ingredients in the product, and it is also a function of the product formulation (e.g., inhaled or oral) and product design (e.g., filter vs. nonfiltered). Moderators of toxicity could include person factors, such as how individuals metabolize toxicants, which could alter exposure to toxicants.

Intensity or extent of use by an individual is associated with the abuse liability of the product (extent to which the product is pharmacologically reinforcing and may produce addiction), product appeal and consumer perception of the product (such as sensory aspects of use, perception of relative safety of the product compared with other products, the packaging, and marketing of the product), and other factors specific to the product, such as the price and availability of a product. Assessment of abuse liability is particularly important because it is the addiction to the product that leads to repeated exposure to toxicants, which ultimately leads to tobacco-caused diseases. Assessment of consumer perception and product appeal is important because they influence not only decisions about whether to use the product but also how the product is used. Moderators of intensity of use can include person factors (such as sex, age, ethnic/racial groups, metabolism of nicotine, and biological response to nicotine), social factors (such as amount of use in the individual's social network), and environmental factors (such as tobacco use restrictions). In addition, whether or not the individual engages in other tobacco or nicotine product use will determine the use intensity and subsequent toxicant exposures. Both the toxicity and intensity of use will determine exposure to toxicants and resulting health risks.

As a final determinant of population harm, an assessment of prevalence (uptake and continued use) of the tobacco product and its effects on all other tobacco use is crucial. Prevalence of product use at a population level is associated with factors similar to those connected to intensity of use (e.g., abuse liability, product appeal, consumer perception, price, and availability). These factors will determine the uptake of the product, that is, initiation and continued use of the product or cessation of product use. Moderators of prevalence of use could include person, social, and environmental (including availability of cessation services) factors. Prevalence of use must also consider the impact of the tobacco product on other tobacco use (e.g., initiation, continued use, and reuptake), including those products that are smuggled and unregulated. Understanding the impact of a product on population harm will require risk assessment and modeling methods that take into consideration all these interacting factors.

Using this framework, the research opportunities addressed in this article are primarily focused on testing the toxicity and potential health effects, examining the abuse liability and product appeal and consumer perception of a product and assessing the extent of uptake, continued use, and pattern of product use and other tobacco use. These topics will be touched upon in the four main areas covered in this paper: modified risk products, products used to treat tobacco dependence, tobacco product standards, and consumer perception testing. Identifying and addressing research questions in these areas will help to enable good science to guide the implementation of tobacco product evaluation so that sound policy decisions are made that will benefit overall public health.

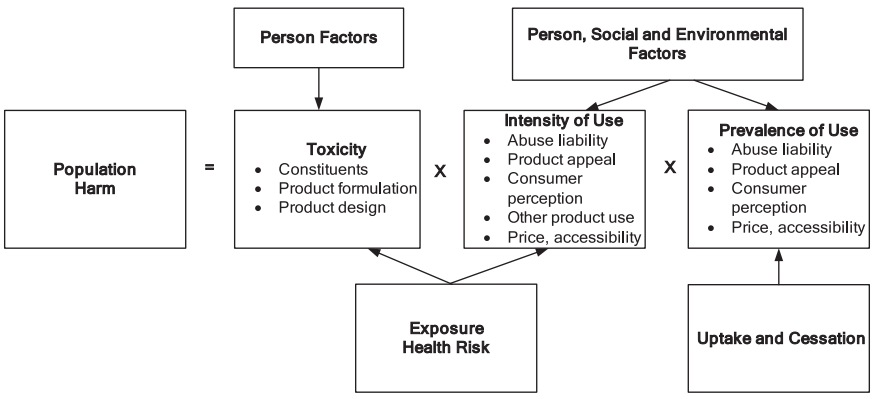

Figure 1. Components to assess population harm (modified from Hatsukami & Parascandola, 2010).

Modified Risk Products

What the Law Provides

A modified risk product is defined as "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products." Section 911, Modified Risk Tobacco Products, states that "the Secretary shall issue regulations or guidance (or any combination thereof) on the scientific evidence required for assessment and ongoing review of modified risk tobacco products". Regulations and guidance shall "(a) establish minimum standards for scientific studies needed prior to approval to show that a substantial reduction in morbidity or mortality among individual tobacco users occurs . . . or is reasonably likely; (b) include validated biomarkers, intermediate clinical endpoints, and other feasible outcome measures, as appropriate, (c) establish minimum standards for postmarket studies that shall include regular and long-term assessments of health outcomes and mortality, intermediate clinical endpoints, consumer perception of harm reduction, and the impact on quitting behavior and new use of tobacco products, as appropriate; (d) establish minimum standards for required postmarket surveillance, including ongoing assessments of consumer perception; and e) require that data from the required studies and surveillance be made available to the Secretary prior to the decision on renewal of a modified risk tobacco product."

History of Regulation

To date, there has been no precedent for regulating the evaluation of modified risk tobacco products.

What is Known

Modified risk tobacco products have entered the U.S. market with implicit or explicit claims for reduced toxicant exposure or reduced health risk. These products have been modified to reduce exposure to tobacco or smoke toxicants either through different curing processes, blends of tobacco, and in the case of cigarettes, genetic engineering or special filters. One marketed cigarette product not only reduced exposure to some tobacco-specific carcinogens but also to nicotine. Significantly reduced nicotine cigarettes could conceivably lead to cessation or decreased development of dependence, which would thereby reduce the prevalence of tobacco use (Benowitz & Henningfield, 1994; Gray et al., 2005; Hatsukami, Perkins, et al., 2010; Zeller, Hatsukami, & Strategic Dialogue on Tobacco Harm Reduction Group, 2009). Other tobacco products that potentially reduce toxicant exposure include cigarettes that electrically heat rather than burn tobacco to reduce toxicants associated with combustion and oral tobacco products with reduced nitrosamines.

Several papers have been written that provide recommendations and guidance on areas and methods for the evaluation of modified risk product (Hatsukami, Benowitz, Rennard, Oncken, & Hecht, 2006; Hatsukami et al., 2005; Stratton et al., 2001; World Health Organization [WHO] Study Group on Tobacco Product Regulation, 2003) including reports produced by the tobacco industry (Brownawell, 2007; Lewis, 2007; St. Hilaire, 2007). In general, these reports describe modified risk product evaluation as involving an assessment of reduction in toxicants and toxicant exposure and toxicity, reduction in individual health risk, and also impact on population harm, with different weights put on the importance of these areas.

Figure 2 provides a schema for the major areas and sequence for modified risk product assessment that takes into account the various factors that contribute to population harm (modified from Hatsukami et al., 2005). The key population harm–related issues addressed within this schema are the toxicity and extent of health risk associated with use of the tobacco product, whether individuals will try the tobacco product and then become dependent on the product, how the product will be used, and the impact of the product on the general population.

Assessments are divided into premarket and postmarket areas. Premarket testing includes determining the toxicity of the product and involves preclinical (nonhuman) studies on constituent yields of toxicants and in vivo and in vitro toxicological tests. Premarket human studies include laboratory and clinical trials that assess the way the products are used and the effects of this pattern of use on biomarkers of exposure and toxicity or indicators of health effects. Premarket testing also involves assessing the potential uptake of and dependence on the product. Preclinical (nonhuman) studies involve analysis of unprotonated nicotine and other potential reinforcing constituents and product design features or additives that may contribute to the product's reinforcing effect. Preclinical (nonhuman) studies may also involve conducting in vivo animal abuse liability testing. Premarket human studies include human laboratory and clinical studies on product abuse liability associated with the pharmacology of the drug.

Integral in the premarket assessment of tobacco product uptake and use is consumer perception and response to the product design, sensory effects, additives, marketing, and promotion, which will determine the extent of product appeal. In addition, consumer perception testing is critical to determine whether any claims of reduced exposure or reduced health risks, marketing efforts, or packaging of the modified risk product are misleading to the consumer regarding the actual risks or benefits associated with the product's use. Any misleading information may unduly lead to uptake of a product due to erroneous beliefs about the relative health risk of a product.

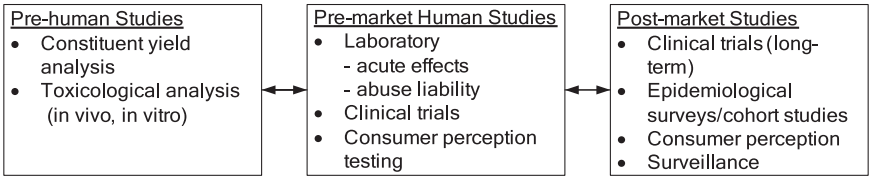

Figure 2. Areas for the assessment of modified risk tobacco products (modified from Hatsukami et al., 2005).

Postmarket studies are aimed at examining actual population effects. They can include long-term clinical trials with the product to assess health effects, epidemiological studies such as longitudinal case-control cohort or cross-sectional studies of the product (which can assess users, nonusers, and users of other tobacco products), and postmarketing surveillance (which can assess any unanticipated consequences and uptake among nonusers, quitters of tobacco products, or among those who were ready to quit). Consumer perception assessment is again important to determine if, once the product is out on the market, perception of the product differs significantly from the premarket assessments. Inherent in conducting these product evaluation studies is the need to consider person (e.g., dependence, gender, age, ethnic-racial differences) and other (e.g., price, smoking restrictions, accessibility) factors that may moderate the abuse liability, consumer perception of the product and product use, and consequent toxicant exposure.

Each product evaluation area will require an assessment of whether the product leads to significantly reduced risk, similar risk, or increased risk compared with currently marketed tobacco products or other comparator products. Additionally, the likely impact of introducing these products to the population as a whole, including their impact on initiation and cessation, needs to be determined.

Research Opportunities

The questions associated with modified risk product evaluation are significant in number and scope. More detailed information on existing methods for testing and research opportunities has also been described elsewhere (Carter et al., 2009; Hanson, O'Connor, & Hatsukami, 2009; Hatsukami et al., 2009; Johnson, Schilz, Djordjevic, Rice, & Shields, 2009; O'Connor et al., 2009; Rees, Kreslake, Cummings, et al., 2009; Rees, Kreslake, O'Connor, et al., 2009). It is important to note that not all these questions need to be addressed by research prior to the implementation of regulatory actions (Samet, McMichael, & Wilcox, 2010). Some of these issues require a development of consensus based on existing data.

Toxicity, toxicant exposure, and potential health risks: (1) *Constituent analysis*: (a) What constituents need to be measured; (b) What should be the comparator for the modified risk product (e.g., the most widely purchased conventional tobacco product, other modified risk products, "ultralight" cigarette products for cigarettes, and/or standard cigarette or standard oral tobacco product); (c) What is the best way to measure constituent yields (e.g., International Organization for Standards and/or Health Canada Intensive smoking methods, human puff profiles that are reflective of use characteristics of consumers, or others); and (d) What are the dose–response relationships between levels of toxicants with levels of exposure, toxicity, and with disease risk? (2) *Toxicological analysis (in vivo and in vitro)*: (a) What constituents should be tested and (b) What in vivo and in vitro methods are necessary for testing tobacco products and are these methods predictive of the extent of toxicity in humans? (3) *Human laboratory and clinical trial analyses*: (a) What are the most appropriate methods (e.g., recruitment methods, instructions for product use, control or comparator group, duration) and measures to assess toxicant exposure and toxicity; (b) What validated biomarkers should be used to demonstrate reduced risk; and (c) What variables or moderators influence response to a product)? (4) *Long-term postmarket analysis*: Questions are similar to human trials above with the addition of identifying critical health outcomes and intermediate clinical endpoints (e.g., health-related quality of life, visits to physicians, hospitalizations, days sick from work, or hypertension, metabolic syndrome, diabetes, and other disease states or diagnosis).

- *Abuse liability testing*: (1) *Laboratory analysis*: (a) What validated laboratory methods and measures should be used to assess abuse potential and acute effects of tobacco products and are these methods reflective of the extent to which a consumer may become addicted to the product; (b) What should be the comparator product(s); and (c) What moderating and mediating influences need to be considered when examining the abuse liability of a product in the laboratory? (2) *Clinical trial and postmarket analyses*: (a) What outcome variables should be used to assess abuse liability (e.g., amount of product use, persistence of product use, misuse of the product, strength of subjective responses to the product) and (b) What moderating variables should be considered?

- *Consumer perception testing:* (1) *Human laboratory, clinical trial and post-market analyses*: (a) What methods and criteria (outcome measures) are needed to demonstrate that a proposed label or marketing of a product touting exposure reduction will not mislead the consumer to believe that the product "has been demonstrated to be less harmful or has been demonstrated to present less risk than one or more other commercially marketed tobacco products" and (b) What measures and methods can be used to assure that the advertising or labeling concerning modified risk products "enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all the diseases and health-related conditions associated with the use of tobacco products?".

- *Postmarketing surveillance (e.g., pattern of product use, health outcomes, and population effect)*: 1) What should be measured? Key measures could include (a) the characteristics of the population using the product, prevalence, and amount of product use; (b) consumer perception of the product; (c) the impact of the modified risk product on overall tobacco use, including initiation of tobacco use, relapse to tobacco, and continued use of tobacco in consumers initially interested in quitting because of its perceived safety; (d) effects of the product on biomarkers of exposure and health risk; and (e) any other adverse or unanticipated effects due to the introduction of the product; (2) How should postmarketing surveillance occur (e.g., phone surveillance, Internet, amount of products sold)? (3) Who should conduct postmarketing surveillance and does this source affect responses to the results of the surveillance; and (4) What criteria should be used to demonstrate that the product results in greater or reduced population harm?

Products Used to Treat Tobacco Dependence

What the Law Provides:

In Section 918, Drug Products Used to Treat Tobacco Dependence, the Secretary is encouraged to consider (a) designating

products for smoking cessation, including nicotine replacement, for fast track review and approval; (b) approving nicotine replacements for extended use; and (c) reviewing nicotine replacements for other indications, such as craving relief or relapse prevention. In addition, FDA must submit a report to Congress that examines the "best way to regulate, promote, and encourage the development of innovative products and treatments to better achieve (a) total abstinence from tobacco use; (b) reductions in consumption of tobacco; (c) reductions in the harm associated with continued tobacco use."

History of Regulation

Historically, the only tobacco-related products that have been regulated by the FDA are pharmaceutical agents for smoking cessation. Nicotine in its pure form, unlike nicotine within tobacco, has ordinarily been considered a drug and has been subject to FDA regulatory authority. Nicotine gum was the first pure nicotine medication manufactured (Ferno, 1973) and subsequently approved by the FDA in 1984 to help smokers quit. Since then, four additional nicotine delivery systems have been approved for cigarette cessation, and three (gum, patch, and lozenge) are available over the counter. It is important to note that the methods used by the FDA for determining efficacy (e.g., 1-year follow-up) have never undergone rigorous review by the scientific community.

Efforts to sell nontobacco nicotine delivery systems that are not indicated for cessation have had mixed outcomes. An early nicotine delivery system called "Favor" was forced from the market in 1985 because it was a drug delivery system (and it was eventually licensed, modified, and tested successfully as a cessation product—the nicotine inhaler; Leischow, 1994). More recently, the so-called "e-cigarette," which heats a nicotine, propylene glycol, and flavoring mix so that the user can puff to get nicotine—has run into regulatory challenges. Many view this product as a nicotine delivery system. FDA's efforts to block the importation of the e-cigarettes and to regulate them as a drug or medical device was struck down by a ruling by the U.S. District Court for the District of Columbia (Civ. No. 09-cv-0771 [RJL]). That ruling was upheld in U.S. Court of Appeals on the grounds that the nicotine in the product is derived from tobacco, and no therapeutic claims are being made.

What is Known

Some countries (e.g., UK and France) have taken a regulatory position that the risk of using nicotine replacement products is so low, particularly relative to tobacco products (McNeill, Foulds, & Bates, 2001; Royal College of Physicians, 2007) that their use in ways that have not been proven by new studies has been allowed (e.g., using NRT to reduce smoking and use of NRT by adolescents and pregnant women). In the United States, however, the FDA has required each new potential modification to undergo additional testing. Nicotine replacement products have been shown to be effective to help smokers quit when they are used as approved (Fiore et al., 2008), but the impact of new indications such as extended use or specifically for craving relief is unknown. On the other hand, medicinal nicotine products have been tested to reduce the amount of cigarette smoking (Hughes & Carpenter, 2006; Silagy, Lancaster, Stead, Mant, & Fowler, 2004). Although the results show a significantly greater amount of cigarette reduction with the use of the active medicinal nicotine compared with placebo product and potentially a greater facilitation of abstinence (Hughes & Carpenter, 2006), whether this reduction leads to greater cessation compared with an immediate quit smoking approach is unclear. Furthermore, a significant reduction in cigarette smoking may not necessarily translate to a significant reduction in exposure and disease risk (Hatsukami et al., 2006; Hecht et al., 2004). Even with limited scientific data, some organizations (e.g., New York State, SRNT, ATTUD) have petitioned for changes in labeling that would support more flexible use of nicotine replacement products on the grounds that risk of using those products is far lower than tobacco products.

With regard to tobacco products, to date, two products are worthy of study to determine whether they lead to significant reductions in tobacco toxicant exposure, tobacco use, or cessation. These products would include tobacco products that contain significantly lower levels of nicotine (levels that render these products nonaddictive) or low-nitrosamine oral tobacco products for smokers (Hatsukami, Ebbert, Feuer, Stepanov, & Hecht, 2007; Zeller et al., 2009). Several studies have examined the use of very low nicotine content cigarettes on cessation. In one small trial of smokers uninterested in quitting, a gradual reduction in nicotine content of cigarettes eventually led to about a 25% cessation rate (Benowitz et al., 2007). In another small trial, smokers interested in quitting were randomly assigned to only using cigarettes with 0.05 mg nicotine, 0.3 mg nicotine, or to nicotine lozenge for a period of 6 weeks and then told to quit using all products. The highest cigarette cessation rate was achieved among those assigned to the 0.05 mg cigarettes who differed significantly from those assigned to the 0.3 mg cigarette but not from those assigned to the nicotine lozenge (Hatsukami, Kotlyar, et al., 2010).

Another tobacco product that may reduce harm but is not harmless is oral tobacco, especially if a smoker switches to this product completely. This approach has been the center of controversy, even if scientists acknowledge that oral tobacco products lead to less risk for disease than cigarettes (Zeller et al., 2009). The critical concern is whether endorsing oral tobacco products as safer may lead to greater population harm (Hatsukami, Lemmonds, & Tomar, 2004; Hatsukami et al., 2007) and whether using an oral tobacco product to aid cessation is better than using medicinal nicotine products. To date, no large clinical trial with random assignment to oral tobacco products versus a comparator treatment has been conducted. It is also important to note that oral tobacco products vary dramatically in their level of toxicity (Hatsukami et al., 2007; Richter, Hodge, Stanfill, Zhang, & Watson, 2008; Stepanov, Jensen, Hatsukami, & Hecht, 2008) If oral tobacco products were proposed as a complete substitute for cigarettes, then standards should be established to substantially reduce the toxicants in these products.

Research Opportunities

There are significant research opportunities in developing novel products and methods for achieving abstinence and reducing harm, and these have been described elsewhere (Hatsukami et al., 2007; Zeller et al., 2009). The following describe the most promising areas of research, some of which was described in another article (Zeller et al., 2009).

- *Safety and efficacy measurements*: (1) How should effectiveness and safety be defined when examining new indications for nicotine replacement products; (2) What testing protocols are needed to most rapidly evaluate the safety (toxicity,

abuse liability, and consumer perception) and effectiveness (clinical trials) of nicotine replacement products; and (3) What type of post-marketing surveillance is needed to assure the safety and effectiveness of nicotine replacement products?

- *Population effect measurements*: What risk/benefit criterion should be considered when determining whether to speed review and approve a new indication?

- *New indications*: (1) What are the benefits and risks of long-term use of medicinal nicotine products or any other pharmaceutical products; (2) What are the effects of approving medicinal nicotine products for relief of craving and withdrawal or for the gradual reduction and then elimination of tobacco use?

- *New medicinal products*: (1) Are there more effective and more palatable medicinal nicotine products that can be developed; (2) Can nicotine delivery systems be developed that mimic the rate and delivery characteristics of tobacco and would such products be more addicting than current medicinal products or equally addicting as tobacco products? If so, what risk/benefit criterion should be considered to determine whether and how they can be approved and marketed; and (3) What are novel targets or mechanisms of action for medications and does combining medications with different targets or mechanisms of action improve treatment outcome?

- *Tobacco products for harm reduction*: (1) Can denicotinized cigarettes serve as a cessation tool with and without medicinal nicotine products? What is the impact of these products on a vulnerable population; (2) What is the impact of switching smokers completely to an oral tobacco product? What are the risks of using oral tobacco products as a cessation tool? What would be the population impact if oral tobacco products were considered safer than cigarettes? What safeguards need to be in place?

Tobacco Product Standards

What the Law Provides

Section 907 states that "The Secretary may adopt tobacco product standards . . . if the Secretary finds that a tobacco product standard is appropriate for the protection of the public health." This finding shall be determined by the "risks and benefits of the proposed standard to the population as a whole, including users and nonusers of tobacco products," 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 and decreased likelihood that those who do not use tobacco products will start using the products" . . . . Content of tobacco product standards shall include provisions, where appropriate for "nicotine yields of the product [other than zero]; for the reduction or elimination of other constituents, including smoke constituents, or harmful components of the product."

History of Regulation

Standards for tobacco products can involve additives, nicotine, and other constituents (see FDA Product Standards article). There have been few examples of regulation of these constituents. In the European Union, a directive was issued that cigarettes cannot exceed 10 mg of tar, 1 mg of nicotine, and 10 mg carbon monoxide (Directive 2001/37/EC of the European Parliament and of the Council of June 5, 2001). These levels are measured by the International Organization for Standardization method. A Swedish tobacco company, Swedish Match, has developed their own voluntary standards called Gothiatek, which do not allow specific constituents in their smokeless tobacco products, snus, to exceed certain limits (http://www.swedishmatch.com/en/Snus-and-health/Our-quality-standard-GothiaTek/GothiaTek-standards/, downloaded September 2010). Additionally, the manufacturing of snus "falls under the Swedish Food Act and additives used are approved for use in foods" (http://www.swedishmatch.com/en/Snus-and-health/Our-quality-standard-GothiaTek/, downloaded September 2010).

The WHO Study Group on Tobacco Product Regulation under the Framework Convention on Tobacco Control has proposed mandated lowering of toxicants in cigarette smoke (Burns et al., 2008; WHO, 2008). As an initial phase of regulation, nine constituents have been targeted for regulation and include acetaldehyde, formaldehyde, acrolein, benzene, benzo[*a*]pyrene, 1,3-butadiene, carbon monoxide, and the tobacco-specific nitrosamines *N*′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The constituents would be regulated based on concentrations per milligram of nicotine, and the Health Canada intense smoking regimen is recommended for this assessment. The WHO recommended that the initial performance levels be the median values of NNK and NNN for brands on the market and 125% of the median for the other toxicants. In addition, disclosure and monitoring of acrylonitrile, 4-aminobiphenyl, 2-aminonaphthalene, cadmium, catechol, crotonaldehyde, hydrogen cyanide, hydroquinone, and nitrogen oxides were recommended (Burns et al., 2008).

There has been no history of nicotine regulation in tobacco products, although a proposal was made in 1994 to reduce levels of nicotine in all marketed cigarettes to nonaddictive levels to prevent the development of dependence among initiators of tobacco products (Benowitz & Henningfield, 1994). This proposal was considered to be technically feasible by the American Medical Association and British Medical Association, but endorsement as a policy measure would be contingent on research that would demonstrate no greater individual and population harm (Henningfield et al., 1998). More recently, an article was published that provides an overview of the literature on reduced nicotine cigarettes (Hatsukami, Perkins, et al., 2010). The authors of this article concluded that the existing literature is supportive of moving forward with providing the science base for a policy that considers reducing levels of nicotine in cigarettes. Recommendations were made for a research agenda that includes examining cigarette design features and constituents other than nicotine that may contribute to the reinforcing effects of cigarettes; identifying threshold dose(s) for nicotine addiction and factors that may moderate this threshold dose; determining the best method to reduce nicotine in cigarettes (schedule of dose reduction and duration of reduction at each dose) and consequences associated with reducing nicotine in cigarettes (e.g., compensatory smoking); identifying methods that might mitigate any adverse consequences; and modeling public health

impact should the reduction in nicotine is considered a viable policy approach.

What is Known

Few studies exist that have directly tested the impact of product standards. To date, the data show that the 10 mg tar–1 mg nicotine–10 mg carbon monoxide standards produce no appreciative reduction in exposure to toxicants because compliance with these mandated yield reductions by manufacturers was primarily achieved through increasing filter ventilation; compensatory smoking is easily achieved with cigarettes that reduce yields through filter ventilation (O'Connor, Cummings, Giovino, McNeill, & Kozlowski, 2006). As a result, the study's authors proposed banning filter vents along with the mandated constituent reductions. Although health risks associated with Swedish snus appear to be less than oral tobacco products with higher tobacco-specific nitrosamine levels that are consumed in other countries, no direct comparisons have been made to determine differences in relative risks across products with differing tobacco-specific nitrosamines or other toxicant levels (Hatsukami et al., 2007). To date, no study has been conducted on the performance standards recommended by the WHO.

With regard to reducing nicotine in cigarettes, two small-scaled studies have examined the effects of gradually reducing levels of nicotine in cigarette products (Benowitz, Jacob, & Herrera, 2006; Benowitz et al., 2007). These studies show that gradually reducing the levels of nicotine content in cigarettes results in minimal compensatory smoking behavior, no increased exposure to toxicants, reduction in dependence, and potential facilitation of cessation in smokers who are uninterested in quitting. One study examined the effects of reduced nicotine cigarettes among smokers who were interested in quitting smoking (Hatsukami, Kotlyar, et al., 2010). In this study, those subjects who were immediately switched to smoking substantially reduced nicotine cigarettes showed no compensatory smoking, reduced toxicant exposure, reduced dependence, and a cessation rate that was similar, if not slightly higher, than medicinal nicotine products.

Research Opportunities

The research opportunities that are associated with additives, nicotine, and other constituents are described in the articles published on FDA Product Standards (Hecht, 2011) and by Hatsukami, Perkins, et al. (2010). The following areas represent additional research questions:

- *Toxicity and potential health risks*: What are the effects of establishing tobacco product standards on tobacco use behavior and on validated biomarkers of exposure, effect, and health risk?
- *Consumer perception*: How does public knowledge of FDA-imposed tobacco product standards affect consumer perception and use of the tobacco products among youth, tobacco users, former users, and nonusers? (See "Consumer perception testing" section for additional research opportunities.)
- *Pattern of product use and population effects*: How do we optimally measure and monitor population effects after tobacco product standards have gone into effect? What are the critical outcome variables (e.g., prevalence of tobacco use, initiation of tobacco product use, continued use of the tobacco product in smokers initially interested in quitting, relapse to tobacco product use, biomarkers of exposure and health risks, unintended consequences such as demand for contraband) and moderator variables (e.g., age, sex, race/ethnicity, socioeconomic status, vulnerable comorbid populations)?

Consumer Perception Testing

What the Law Provides

Section 904 requires that the Secretary publish a list of harmful and potentially harmful constituents to health, including smoke constituents, in each tobacco product by brand and by quantity in each brand and subbrand. The Secretary is also required to conduct periodic consumer research to ensure that the list "is not misleading to lay persons." Within five years, the FDA must report back to Congress on the results of the research and with recommendations on whether publication of the list should be continued or modified.

History of Regulation

Consumer perception testing has played an important historical role in the regulation of other consumer products. Quantitative consumer research has helped inform governmental policy on food labeling and advertising, and risk perception testing has contributed to consumer product safety policies. In the absence of consumer perception testing, governmental officials did not realize the harm that would be caused by the sanctioning of the marketing of "light" and "low-tar" cigarettes. There are important historical lessons to be learned about how consumer research, when mandated and conducted effectively, is an essential tool in the regulation of consumer products and the creation of regulatory policy.

What is Known

Although many states, countries, and localities require that tobacco companies report product constituents to governmental authorities, the public's access to this information has been quite limited. There is considerable research that demonstrates that although consumers feel that they should have access to information about tobacco constituents (Carter & Chapman, 2006; Chapman, Wilson, & Wakefield, 1986; Phoenix Strategic Perspectives, 2006), they are very likely to be confused about the meaning of the data. For example, a survey of Canadian smokers demonstrated that many believe that chemical constituents of cigarettes are man-made substances that are added to tobacco and not inherent components of the product and its combustion (Environics Research Group Limited, 2003). Also, information about ingredients in the cigarette is taken to mean ingredients that are absorbed when the cigarette is smoked (Ipsos-Eureka Social Research Institute, 2009; Phoenix Strategic Perspectives, 2006), when in fact, smoking patterns and individual biological characteristics can affect what is actually absorbed. Given that cigarettes contain 5,000 constituents in tobacco smoke (Rodgman & Perfetti, 2009), finding an effective way to convey useful information to consumers is a challenge.

Many studies of consumer perceptions of tar and nicotine labeling on cigarette packages and advertising have concluded that providing quantitative information about various tobacco products is detrimental to public health because it is used by the consumer to make inaccurate judgments about relative harmfulness of different brands. Specifically, studies have shown that smokers report choosing among brands with varying tar labels in the mistaken belief that one cigarette will cause them fewer health problems than another (Borland et al., 2004; Cummings, Hyland, Bansal, & Giovino, 2004; Kozlowski & Pillitteri, 2001; Shiffman, Pillitteri, Burton, Rohay, & Gitchell, 2001a, 2001b). Indeed, the tar and nicotine ratings were used as marketing tools by tobacco companies to convey what is now known to be the false information that "low-tar" cigarettes are less harmful than regular cigarettes (Pollay & Dewhirst, 2002; Wakefield, Morley, Horan, & Cummings, 2002). However, the consumer misperception is due to the fact that cigarette design and testing methods were such that consumers were likely to end up absorbing greater levels of tar and nicotine than was indicated on the package (Jarvis, Boreham, Primatesta, Feyerabend, & Bryant, 2001; National Cancer Institute, 2001). It is also the case that most consumers lack the knowledge to properly evaluate numeric differences in different constituents in different brands (Phoenix Strategic Perspectives, 2006). In light of these findings, the WHO's Framework Convention Alliance recommends that Parties to the FCTC "not require quantitative or qualitative statements about tobacco constituents and emissions on packages or labeling that might imply that one brand is less harmful than another . . . ." (Article 11, para 33).

Researchers have concluded that the strategy more likely to be understood is one that uses simple descriptive information about dangerous constituents on the product's label—such as the one in the Figure 3 (www.tobaccolabels.ca; D. Hammond, personal communication, May 11, 2009).

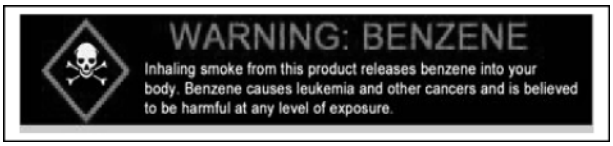

Figure 3. Example of product label for toxic tobacco constituents.

Results of research on the impact of constituent yields on tobacco labels could be seen to support a recommendation that the Secretary not disseminate the published list of constituents to lay people. However, not providing such information may convey the impression that all tobacco products are equally harmful, an impression that is inaccurate and that runs counter to current research, which acknowledges a continuum of risk among tobacco products (Sweanor, Alcabes, & Drucker, 2007; Zeller et al., 2009). The requirement that the list be published, at least initially, offers a number of research opportunities that could inform the consumer research that is also mandated by the law.

Research Opportunities

Research opportunities related to consumer misperception deal with the variety of ways that misperception may be manifested.

- What constitutes an accurate perception of the relative harmfulness of different brands and types of tobacco products? This standard is required before misperception can be assessed. The standard is likely to change as new products develop and as research results on toxicants are forthcoming.
- What methods for presenting information about tobacco constituents can be developed that result in consumers having an accurate understanding of the relative harmfulness of the various products?
- What types of communication about product constituents best prepare the public for evaluating new products that come onto the market, which may have meaningful reductions in some toxic constituents?
- What validated methods should be used to assess the impact of communication styles on participants' ratings and rankings of product harmfulness (e.g., focus groups, experimental studies of samples of convenience, population surveys)?
- What areas of measurement are critical for establishing a baseline against which potential changes can be measured: for example, (a) perceptions of the relative harmfulness to health of regular use of a variety of tobacco products; (b) beliefs about the elements of tobacco or tobacco use that cause harm to health (e.g., additives to tobacco, tobacco itself, the composition of tobacco smoke); (c) perceived personal relevance of information about tobacco constituents; (d) awareness of the availability of information about constituents; and (e) beliefs about the identity and credibility of the source of information about product constituents.
- How do correct perceptions of the relative harmfulness of product brands and types affect consumer choice among products?
- How does misperception of the relative harmfulness of product brands and types affect consumer choice among products?

Summary and Conclusions

Testing the impact of modified risk products, new indications for medicinal nicotine products or novel products used for cessation, tobacco product standards, and consumer perception of the toxicant levels of products all require an assessment framework and tools. This framework cannot be limited to just describing the components for product testing. The impact of a product must be considered in the context of other regulatory and tobacco control activities and policies as well as tobacco industry activities. For example, the effect of introducing a product into the market may also be affected by the amount of taxation, educational campaigns, regulation of packaging and labeling, marketing efforts, and tobacco company discounts for the product. The research gaps or lack of consensus pertaining to the assessment of tobacco products primarily are related to the following questions:

(1) What should be measured?

(2) How should we measure it?

(3) What are the validated tools for measurement?

(4) What are significant moderator variables that influence response to the product?

(5) How do we know that we have substantive reduction in toxicants, exposure to toxicants, health risk, and harm to the public?

(6) How do we know that the consumer is not misled by claims that are made or by the information that is provided about tobacco products?

(7) What criteria do we use to determine that a proposed approach or product does not have a negative impact on public health? By what criteria do we assess risks versus benefits and how do we weigh any ethical considerations that arise from any regulatory actions (e.g., benefits one population but not another).

(8) What safeguards and postmarketing measures need to be put in place so that harm would be minimized and optimally, public health would benefit?

Addressing all these gaps through research may not be required. As an initial step, we may need to come to a consensus on the best available tobacco assessment tools that we currently possess. As much public harm could be done by waiting until we have all the necessary validated tools and measures before making decisions on tobacco product standards and modified risk products as by making a decision with insufficient science. Therefore, tobacco product testing is likely to be an iterative process, where we learn from feedback how to improve upon existing approaches. What is critical is to have a solid postmarketing surveillance protocol in place so that impact of decisions can be determined in a rapid manner, considered in the context of the whole tobacco control landscape and adjusted accordingly.

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