



June 4, 2012

**COMMENTS ON GUIDANCE FOR INDUSTRY ON MODIFIED RISK
TOBACCO PRODUCT APPLICATIONS UNDER SECTION 911 – Docket ID: FDA-2012-
D-0071**

The undersigned organizations submit these comments on the Guidance for Industry promulgated in the above-designated docket concerning the submission of Modified Risk Tobacco Product Applications (“MRTPA”) under section 911 of the Family Smoking Prevention and Tobacco Control Act of 2009 (Public Law 111-31) (“Tobacco Control Act”).

Principal Conclusions and Recommendations

An overwhelming array of evidence demonstrates that, in the absence of effective regulation, tobacco product manufacturers are likely to make health claims about their products that are untrue or misleading. Even if such claims are artfully phrased to avoid being technically inaccurate, these claims may be harmful to public health if they lead consumers to switch to new hazardous products. These products are equally dangerous, or at the least far more dangerous than quitting altogether. They discourage smokers from quitting and encourage non-users to initiate the usage of tobacco products. Over the course of many years, such claims have misled millions of consumers and caused millions of unnecessary deaths. Despite the enactment of the Tobacco Control Act, the major tobacco companies continue to make false and misleading health claims that lead people to continue to use hazardous tobacco products instead of quitting.¹ The statutory findings and the text of the statute demonstrate that the essential purpose of Section 911 is to protect consumers against such claims and rigorous enforcement of Section 911 will be needed to do so.

The principal conclusions and recommendations reached by these comments are as follows:

1. Overall, the provisions of the guidance are appropriate, consistent with the statutory requirements and the underlying purposes of the statute, and consistent with the recommendations made by the Institute of Medicine.² The information and studies called for by the guidance represent the minimum needed for the Food and Drug Administration (FDA) to carry out its responsibilities.

¹ See discussion of the use of color coding of cigarette packs, *infra* at 11, 22-23.

² Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December, 2011.

2. The guidance should incorporate in greater detail the recommendations made by the Institute of Medicine and explicitly state that FDA will follow these recommendations in evaluating MRTPAs.
3. FDA should convert the guidance into enforceable regulations as soon as possible.
4. The guidance should incorporate the recommendation made by the Institute of Medicine that an expected sequencing of studies should be required. Preclinical work is completed and submitted to the FDA before clinical (human subjects) work commences and that there is a reasonable expectation based on preclinical work that a reduction or lack of harm will be seen in humans.
5. The guidance should incorporate the recommendation made by the Institute of Medicine that independent third parties, approved by FDA, should undertake one or more key functions, including the design and conduct of research, oversight of specific studies and distribution of sponsor funds for research.
6. The guidance should make clear that all advertising and promotional material for a modified risk tobacco product (MRTP) must be submitted to FDA in advance of its use and may not be used in the absence of a prior determination by FDA to ensure that such materials are consistent with the MRTP order. This requirement should be applied to all such materials, including those developed and used after the grant of an order.
7. FDA should enforce Section 911 to remedy the ongoing misrepresentation by major tobacco manufacturers that cigarettes in color-coded packs are less harmful than other cigarettes.

These comments also make the following additional recommendations:

8. The guidance should explicitly state that the burden of proving each and every element is on the applicant.
9. Consumer perception studies must be conducted both before the grant of an application and as part of post-market monitoring in order to determine how consumers actually understand modified risk messages after a product is marketed.
10. The guidance should make it clear that any order granting an application permits only the precise claim authorized in the order to be made about the product. Any departure from the text or method of presentation of such claim is not authorized.
11. Testing for consumer perception should include testing to determine the effect of context and other non-verbal messaging on such perception.

12. Benchmarks for comparison recognized by the guidance should be expanded to include examination of the extent to which the grant of an MRTP order might serve for non-users of tobacco products as a gateway to the use of other tobacco products.
13. Benchmarks for comparison recognized by the guidance should be expanded to include examination of the extent to which the grant of an MRTP order might lead those who have quit using tobacco products to reinitiate their usage.
14. Greater emphasis should be placed on the importance of considering the effects of granting an MRTP order on demographic groups that may be disproportionately affected by the marketing of such products either because they are likely to be targeted in the marketing of such products or because they may otherwise be likely to be disproportionately represented in the market for the product. In such cases, oversampling of these groups may be warranted in the testing of such products. To accomplish this goal, the guidance should clarify that the range of consumer perception studies presented by an applicant must yield evidence about consumer perception separately for each of the major target groups for advertising and marketing of the product and each of the groups most vulnerable to modified risk claims. Moreover, post-market studies should be designed to provide evidence about the effect of modified risk claims on any demographic group disproportionately represented in the market for the product.
15. FDA should develop adequate procedures to ensure that MRTP applications are made publicly available, as required by the statute, while they are pending and that claims of commercial confidentiality do not preclude public understanding of such applications and meaningful public participation in FDA's evaluation of such applications.
16. No MRTP order should be granted without submission of full testing data regarding all harmful and potentially harmful constituents designated by FDA pursuant to Section 904, without regard to any limitations on data submission requirements contained in the guidance on harmful and potentially harmful constituents, as well as any other constituent the FDA identifies.
17. FDA should require in the application process the submission of all marketing analysis and product development materials developed by or for an applicant concerning the product at issue and any related products.
18. FDA should require all MRTP sponsors to place all data generated in the development and marketing of the MRTP in a public repository selected by FDA, as recommended by the Institute of Medicine.
19. Appropriate limits should be placed on health claims used in consumer perception tests by or on behalf of a tobacco manufacturer, in order to avoid broader dissemination of such claims than is necessary for the conduct of the tests.

Introduction

Section 911 establishes the standards under which FDA is to consider applications to market tobacco products when the manufacturer seeks to make a claim that the product presents a reduced risk of harm and disease compared to another tobacco product, or, alternatively, a claim

of reduced exposure to harmful constituents.³ This section is extremely important because, as Congress recognized when the Tobacco Control Act was enacted, such claims strongly influence consumer perceptions and change consumer behavior. The specific tobacco products consumers buy and use is heavily influenced by health claims made about these products. Because health claims affect consumer behavior so profoundly, there is a compelling governmental interest in establishing a regulatory regime that ensures, to the greatest extent possible, that any such claims actually benefit the public health. The burden of tobacco on disease, death and health care costs in the United States must be reduced, not increased, by the introduction of modified risk tobacco products. The fundamental purpose of Section 911 is to ensure that any such claims are factually true and not misleading (i.e., that the product about which claims are made does, in fact, present a lower risk of harm to the individual) *and* that such claims will lead to a net benefit to the public health of the population as a whole.

As a threshold matter, it is important to note that both modified risk tobacco products and modified exposure tobacco products are, by definition, products as to which modified risk or modified exposure claims are made. If no such claims are made, the requirements of Section 911 do not apply to the product. A product may qualify to be marketed as a new product or an existing product, but that does not mean that a manufacturer can make modified risk claims about it. Section 911 establishes strict and specific requirements for such claims, and no modified risk claim can be made for any tobacco product in the absence of an order issued under Section 911. Section 911 is not designed to prevent products from being marketed; rather, it is designed to ensure that no health claims are made about such products, unless those claims are demonstrated to be true, not misleading, and likely to benefit the public health of the population as a whole.

When Congress enacted Section 911, it was acutely aware of recent history in which tobacco product manufacturers made false claims of reduced harm and reduced exposure. Such claims persuaded many consumers who otherwise might have quit to instead switch to products that were not in fact any safer or less addictive and which presented no reduction in exposure to harmful constituents. An overwhelming body of evidence demonstrates that the tobacco product manufacturers who made these claims were aware that they were untrue at the time; that they made these claims with the express purpose of persuading smokers to continue to use tobacco products rather than quitting; and that they succeeded in achieving their objective. One purpose of Section 911 is to ensure that this history is not repeated.

In evaluating applications under Section 911, FDA should recognize that most applications will be coming from the same manufacturers who have misrepresented the health effects of their products for decades and that the same incentives for misrepresentation continue to exist. Moreover, there is substantial concern that these manufacturers are continuing to make modified risk claims—in violation of Section 911—even now. FDA should therefore not only ensure that its guidance serves the purposes of Section 911, but also that the provisions of Section 911 are properly enforced when unauthorized claims are made.

A manufacturer applying under Section 911 must demonstrate with scientific evidence that such claims will lead to a net benefit to the public health of the population as a whole. Because no tobacco product is safe, the best alternative for those who do not use tobacco products

³ Section 911 establishes standards for modified risk tobacco products and also establishes an additional set of standards for “modified exposure tobacco products.” References in these comments to “modified risk tobacco products” also include “modified exposure tobacco products.” unless expressly noted to the contrary. The term “health claims” as used in these comments likewise encompasses both modified risk claims and modified exposure claims.

is not to initiate usage, and the best alternative for those who use tobacco products is to quit using tobacco entirely. To the extent that modified risk claims contribute to initiation of use or discourage cessation by those who would otherwise quit, such claims are detrimental to public health. Modified risk claims are potentially beneficial to the public health *only* to the extent that they affect the use behavior of those who would not otherwise be abstinent or quit. The statute requires FDA to establish a regime that will enable it to evaluate the likely net effect of modified risk claims and properly places the burden of proving net public health benefit on those seeking to make the claim.

The guidance issued in this docket is intended to inform manufacturers and the public of the evidence that must be submitted to meet the statutory standards established under Section 911. The criteria were intentionally made stringent because the products at issue are known to be lethal and the consequences of permitting health claims to be made are potentially vast and far-reaching.

The draft guidance that has been promulgated should be evaluated in light of the findings made by Congress when it enacted the statute, the history of health claims for tobacco products that underlay the statutory provisions,⁴ recommendations made by the Institute of Medicine in December 2011 pursuant to statutory direction, the express language of section 911, and the practical consequences likely to flow from adoption of the guidance.

I. Background

A. The Relevant Statutory Findings

Section 911 is one of several sections of the Tobacco Control Act that grant authority to FDA to regulate tobacco products and claims made in the advertising and promotion of tobacco products. Congress made numerous express findings that underpin the enactment of Section 911 and explain its purpose.

- The use of tobacco products constitutes a major public health problem that is substantially influenced by consumer perceptions regarding the health risks of tobacco products. Sec. 2 (13) (37),(40)
- Such perceptions are profoundly affected by claims made by tobacco product manufacturers regarding the health risks of their products and the exposure posed by such products. Sec. 2 [41]
- “Consumers have misinterpreted advertisements in which one product is claimed to be less harmful than a comparable product, even in the presence of disclosures and advisories intended to provide clarification.” Sec. 2(41)

⁴ The most comprehensive account of this history is that contained in the factual findings made by the United States District Court for the District of Columbia in *U.S. v. Philip Morris, USA, Inc.*, 449 U.S. 1 (D.D.C. 2006), *aff'd in relevant part*, 566 F. 3d 1095 (D.C. Cir. 2009), *cert. denied*, 130 S. Ct. 3501 (2010) and in National Cancer Institute Monograph 13, *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine* (2001). See *infra*, at pp. 8-9.

- Unless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health. . . .” Sec. 2(37)
- The dangers of products sold or distributed as modified risk products, that do not in fact reduce risk, are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product.” Sec.2(40)

On the basis of these findings concerning the detrimental effects of misleading statements regarding modified risk products, Congress concluded that

- “Permitting manufacturers to make unsubstantiated statements concerning modified risk tobacco products, whether express or implied, even if accompanied by disclaimers would be detrimental to the public health” Sec. 2(42); and
- “the only way to effectively protect the public health from the dangers of unsubstantiated modified risk tobacco products is to empower the Food and Drug Administration to require that products that tobacco manufacturers sold or distributed for risk reduction be reviewed in advance of marketing, and to require that the evidence relied on to support claims be fully verified.” Sec. 2(43).

Congress described the nature of the findings FDA is expected to make before it permits modified risk claims to be made. It found that:

- It is essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria, and will benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.” Sec. 2 (36).

Congress also explained the basis for its designation of the FDA as the agency to perform this regulatory function. It recognized that the FDA had the “scientific expertise to . . . evaluate scientific studies supporting claims about the safety of products and to evaluate the impact of labels, labeling, and advertising on consumer behavior in order to reduce the risk of harm and promote understanding of the impact of the product on health.” Sec. 2 (44).

These unusually specific statutory findings set forth in detail the purposes of Section 911 and the assignment given to the FDA. Moreover, Congress further elaborated the regulatory framework for FDA’s decision making by creating a highly detailed set of statutory criteria in Section 911. Congress directed FDA to “...issue regulations or guidance . . .on the scientific evidence required for assessment and ongoing review of modified risk tobacco product.” Sec. 911 (l)(1) The guidance at issue here is intended to provide further specification of the requirements established in the statute.

In addition to the specific statements of legislative purpose and the highly detailed provisions of the statute, Congress instructed FDA to develop its regulations or guidance implementing section 911 “in consultation with the Institute of Medicine, and with the input of other appropriate scientific and medical experts, on the design and conduct of such studies and surveillance.” Sec. 911(l)(2) Pursuant to this direction, the Institute of Medicine appointed a committee of medical experts that held extensive hearings on these issues and issued a detailed

report in December 2011, *Scientific Standards for Studies on Modified Risk Tobacco Products*. This report represents the most complete and authoritative statement by the scientific community on the matters addressed in these guidelines.

B. The Relevant History

No provision of the Tobacco Control Act was more profoundly influenced by recent history — and a determination to learn from the mistakes of the past — than Section 911. The provisions of Section 911 are based on a massive evidentiary record evaluating the nature and effect of health claims made by tobacco product manufacturers for more than fifty years. Overwhelming evidence demonstrates that such claims have caused millions of Americans to initiate cigarette smoking, which otherwise would not have done so, and caused millions of American smokers who otherwise would have quit to continue to smoke. In addition, overwhelming evidence demonstrates that permitting such claims to be made has caused millions of preventable deaths.

The evidence comes from a multiplicity of authoritative sources.

1. U.S. v. Philip Morris

In the landmark case of *U.S. v. Philip Morris, USA, Inc., supra*, note 3, the U.S. District Court for the District of Columbia compiled a massive evidentiary record regarding the effects of health claims on consumer perception and consumer behavior. This record was based on hundreds of thousands of pages of documents from the files of the tobacco product manufacturers and the testimony of scores of witnesses. The industry had every opportunity to present contrary evidence to the court and presented numerous witnesses and extensive argument. After examining this massive record, the court made voluminous findings that take up 937 pages in the federal reports.⁵ The Court summarized its conclusions as follows:

For several decades, Defendants have marketed and promoted their low tar brands as being less harmful than conventional cigarettes. This claim is false, as these Findings of Fact demonstrate. By making these false claims, Defendants have given smokers an acceptable alternative to quitting smoking, as well as an excuse for not quitting.

U.S. v. Philip Morris, 449 F. Supp. 2d at 430

By engaging in this deception, Defendants dramatically increased their sales of low tar/light cigarettes, assuaged the fears of smokers about the health risks of smoking, and sustained corporate revenues in the face of mounting evidence about the health dangers of smoking.

U.S. v. Philip Morris, 449 F. Supp. 2d at 561.

Moreover, the Court found that

The evidence establishes that the vast majority of people who smoke today want to quit due to health concerns. Defendants accurately perceive smokers' desire to quit as a significant threat to their economic welfare and possibly their existence; obviously, if

⁵ The district court devoted 131 pages of findings to the issue of the false marketing of light and low-tar cigarettes alone. 449 F. Supp. 2d at 430-561.

sufficient numbers of smokers who want to quit actually do so, it will greatly diminish Defendants' earnings.

...[A]s their internal documents reveal, Defendants engaged in massive, sustained, and highly sophisticated marketing and promotional campaigns to portray their light brands as less harmful than regular cigarettes, and thus an acceptable alternative to quitting, while at the same time carefully avoiding any admission that their full-flavor cigarettes were harmful to smokers' health. Defendants knew that by providing worried smokers with health reassurance, they could keep them buying and smoking cigarettes.

Defendants' efforts have been successful. Even though low tar cigarette smokers have a greater desire to quit, their misconception that low tar cigarettes are less harmful dissuades them from doing so. Current research demonstrates that approximately 50% of all smokers of lower tar cigarettes chose such products because they perceive them to be a "healthier" cigarette and a potential step toward quitting....

Defendants use these so-called brand descriptors such as "light," "medium," and "mild" to market their brand extensions as low in tar with full knowledge that a substantial number of smokers interpret these descriptors as indicating a less harmful cigarette.

The misleading nature of Defendants' design and marketing of filtered and low tar cigarettes continues."

U.S. v. Philip Morris, 449 F. Supp. 2d at 859-61 (citations omitted)

In addition, the Court found that "there is a reasonable likelihood that Defendants' RICO violations will continue. . . . Defendants' practices have not materially changed, including: . . . denial of the manipulation of the design and content of cigarettes, suppression of information and research, and claims that light and low tar cigarettes are less hazardous than full-flavor cigarettes." *Id.* at 911

These findings were affirmed by the United States Court of Appeals. The Court of Appeals stated:

[W]e are not dealing with accidental falsehoods or sincere attempts to persuade; Defendants' liability rests on deceits perpetrated with knowledge of their falsity.

The district court in this case did not find liability solely based on the use of descriptors such as "light" and "low tar." The court found that the Defendants orchestrated "highly sophisticated" marketing and promotional campaigns to portray their light brands as less harmful than regular cigarettes. In addition to the misleading use of descriptors, the district court found Defendants public statements are blatantly false in relation to the marketing of light cigarettes. The district court went on to find that as part of the Enterprise's scheme to defraud smokers, Defendants withheld and suppressed their extensive knowledge and evidence of nicotine-driven smoker compensation. These findings reveal that the fraudulent activity surrounding "light" cigarettes was not limited to the use of misleading descriptors.

566 F. 3d at 1095, 1124-25 (D.C. Cir. 2009).

2. NCI Monograph 13

In 2001 the National Cancer Institute issued a 235-page monograph entitled “Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine” (Monograph 13).⁶ The monograph traced the history of the marketing of cigarettes over the course of 50 years, from the 1950s through 2000, and the effect of that marketing on public perception about the risks of smoking during that period and on actual consumer behavior. Monograph 13 presented voluminous evidence showing that for at least 50 years—long predating the introduction of “light” or “low-tar” cigarettes – health claims by tobacco companies had been specifically designed to prevent smokers concerned about their health from quitting. The report concluded that during the 1950s, in response to early reports of links between cigarette smoking and cancer, “advertising . . . promoted filters as the technological fix to the health scare . . . The purported product benefit of this new filtration was obviously the perceived reduction, if not elimination, of cancer and other health risks.” Monograph 13 at 200

The NCI Monograph concludes:

1. Advertisements of filtered and low-tar cigarettes were intended to reassure smokers (who were worried about the health risks of smoking) and were meant to prevent smokers from quitting based on those same concerns.
2. Advertising and promotion efforts were successful in getting smokers to use filtered and low-yield cigarette brands.
3. Internal Tobacco Company documents demonstrate that the cigarette manufacturers recognized the inherent deception of advertising that offered cigarettes as “Light” or “Ultra-Light,” or as having the lowest tar and nicotine yields.

Monograph 13 at 223.

3. 2012 Report of the Surgeon General

The most recent report of the Surgeon General, *Preventing Tobacco Use Among Youth and Young Adults*,⁷ released in March 2012, provides additional evidence that health claims by major tobacco companies, particularly those involving light and low-tar cigarettes, may have increased youth initiation to cigarettes.⁸

Moreover, advertising geared to promoting cigarette smoking as a weight control strategy have long been a staple of tobacco industry promotional strategies. Promotion of products as “slim,” “superslim,” “slim lights,” and “superslim lights” are designed to send a health message to young girls. The report cited evidence that “the widespread belief that smoking is an effective

⁶ National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Tar Machine-Measured Yields of Tar and Nicotine*, Smoking and Tobacco Control Monograph No. 13, November, 2001.

⁷ HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, 2012 <http://www.cdc.gov/Features/YouthTobaccoUse/>

⁸ *Id.* at 531 and sources cited therein.

way to stay thin and control weight is an important predictor of tobacco use among girls.”⁹ Products promoted with these designations continue to be marketed. As a result of consistent messages linking smoking with weight control, a substantial majority of youth, particularly females, believe that smoking controls body weight. However, contrary to young people’s beliefs, smoking by adolescents and young adults is not associated with significant weight loss, and teen smokers are not thinner than nonsmokers.¹⁰ FDA should enforce the provisions of Section 911 to prevent the continuation of health claims based on weight loss.¹¹

B. Recent History

1. Health Claims for Cigarettes

The tobacco industry’s hugely successful promotion and marketing of “light” cigarettes resulted in dramatic increases in the sales of such cigarettes. In 1967, only 2% of cigarette sales in the United States had tar ratings that were 15 milligrams or less. By 2008, 82.6% of all cigarettes sold in the United States had tar ratings that were 15 milligrams or less.¹² It is clear that making health claims has been good business for tobacco product manufacturers, even if those claims are untrue and even if millions of smokers die as a result of believing them.

Recent events have demonstrated that tobacco product manufacturers, recognizing the potential for health claims to affect consumer behavior, may, in the absence of effective regulation, continue to make unsubstantiated health claims for tobacco products.

As noted above, Section 911 prohibited tobacco product manufacturers from marketing cigarettes with descriptors such as “light,” “low” and “mild” effective June 22, 2010. However, prior to the effective date the major tobacco companies implemented a strategic response to perpetuate their deceptive claims by informing retail stores and consumers that the very same cigarettes could be found in “colored packs.” See Int. Sept. 7, 2010 Status Rep. (DN 5828). For example, consumers who previously smoked Marlboro Lights were told that they could now purchase “Marlboro Gold” and “Marlboro Silver.”¹³ A flier sent to distributors told them that Marlboro Lights, the nation’s best-selling brand, would become “Marlboro Gold” and that “Marlboro UltraLights” would become “Marlboro Silver.” Moreover, Philip Morris placed notes on packs of Marlboro Lights reading “Your Marlboro Lights package is changing, but your cigarette stays the same” and directing customers to “in the future, ask for Marlboro in the gold pack.”¹⁴ The other major tobacco product manufacturers also implemented a similar strategy to

⁹ *Id.* at 30-79 and references cited therein and at 112-128; 533.

¹⁰ *Id.*

¹¹ Young girls are of course not the only target of promotions promoting cigarette smoking as a weight-loss strategy. Such campaigns have long targeted women of all ages since the 1920s. *Id.* at 30. “An implied association between smoking and weight control has been used countless times.”

¹² Federal Trade Commission Cigarette Report for 2007 and 2008, issued 2011. <http://www.ftc.gov/os/2011/07/110729cigarettereport.pdf>.

¹³ Duff Wilson, “Coded to Obey Law. Lights Become Marlboro Gold,” *New York Times*, Feb. 18, 2010.

¹⁴ Duff Wilson, “FDA seeks explanation of Marlboro Marketing,” *New York Times*, June 17, 2010.

inform consumers that colored packs corresponded to “light” cigarettes brands they had been smoking.¹⁵

These actions were taken despite the provisions of Section 911(b)(2)(A)(i), which prohibited the sale or distribution of any tobacco product making a modified risk or modified exposure claim, effective on the date of enactment, and despite the provisions of Section 911 (b)(2)(A)(iii), which made it unlawful for any tobacco product manufacturer to “tak[e] any action directed to consumers, through the media or otherwise, other than by means of the tobacco product’s label, labeling, or advertising, *after the date of the enactment of the Family Smoking Prevention and Tobacco Control Act*, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products. . . .”

Such claims are not the only unauthorized health claims the industry has made in recent years. A Vermont court recently found that R.J. Reynolds violated the Master Settlement Agreement by making unauthorized health claims in violation of a provision of that agreement barring Participating Manufacturers from misrepresenting the health effects of tobacco products. In a heavily documented decision, the court found that health claims made by the company regarding its Eclipse brand of cigarettes were “misleading and deceptive because the support relied on was scientifically and medically insufficient.”¹⁶

2. Current market trends and incentives for health claims about non-combustible tobacco products.

While smoking and the use of smokeless tobacco products among youth has declined significantly since the mid-1990s, youth smoking declines appear to have slowed and the use of smokeless tobacco products among youth has increased.¹⁷ This finding suggests smokeless tobacco products are not substituting for smoking but rather are adding to the number of tobacco users. Concurrent use of multiple tobacco products appears to be growing.¹⁸ These trends each point to the potential for increasing the widespread harm of all types of tobacco use and provide the support for FDA taking a rigorous scientific approach and high standards of evidence in its requirements for approval of MRTPAs. The increase in the use of non-combustible tobacco products may in part be the result of consumer responses to the widespread adoption in recent years of clean indoor air policies. In response to these policies, the major tobacco companies have promoted the use of smokeless tobacco products for dual use with combustible tobacco products and encouraged smokers to use smokeless tobacco in situations in which smoking is not an

¹⁵ *Id.*; see also http://www.nytimes.com/imagepages/2010/06/18/business/18tobacco_1.html.

¹⁶ *State of Vermont v. R.J. Reynolds Tobacco Company*, 2010 Vt. Super. LEXIS 11 (Vt. Super. 2010); The Court found that the claims, although deceptive and misleading, were not made in bad faith but noted that it was in the company’s economic self-interest to make such claims in order to maximize sales of its products.

¹⁷ CDC, “Cigarette Use Among High School Students – United States, 1991-2009,” *MMWR* 59(26), July 9, 2010. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5926a1.htm>;

¹⁸ SAMHSA, *The NSDUH Report: Smokeless Tobacco Use, Initiation, and Relationship to Cigarette Smoking: 2002 to 2007*, Rockville, MD: Office of Applied Studies, March 5, 2009, <http://www.oas.samhsa.gov/2k9/smokelessTobacco/smokelessTobacco.pdf>.

alternative.¹⁹ Moreover, during the past several years each of the major tobacco companies has greatly diversified the range of tobacco products it offers. As a result of these developments, the future of tobacco usage in the United States may differ significantly from historic patterns. In a changing marketplace, tobacco product manufacturers are likely to perceive continuing incentives to make health claims for their products.

C. Relevance of the History

The well-documented history --spanning several decades-- of the major tobacco companies' conduct regarding modified risk claims and its impact on consumers is relevant to the appropriateness of the guidance in this docket. That history demonstrates all the following elements.

- Consumers are highly motivated in making decisions regarding their use of tobacco products by their perception of the health consequences of tobacco products.
- Consumers who are likely to consider quitting are those most susceptible to modified risk claims.
- Modified risk claims that affect consumer perception of the health risks of using tobacco products affect consumer behavior and have led many smokers who otherwise would have quit or tried to quit to instead switch to products they falsely believed were less hazardous.
- The major tobacco companies have a long history of making modified risk claims that they know not to be true in order to prevent consumers from quitting. Because the major tobacco companies have done so for many decades, there is every reason to be very concerned that they will, if provided the opportunity, continue to do so in the future.
- The major tobacco companies have demonstrated disregard for the truth in making modified risk claims.
- The major tobacco companies have demonstrated a willingness to distort and suppress scientific evidence that is inconsistent with their modified risk claims.
- The major tobacco companies continue to have massive economic incentives to misrepresent the health effects of tobacco products in order to maintain their market.
- The major tobacco companies have also made claims that, while technically correct, have both misled consumers about the relative safety of different products and have had detrimental impacts on public health because they caused some smokers who might otherwise have quit instead to switch and led other consumers who might not have started to smoke to do so.
- Recent conduct by tobacco product manufacturers demonstrates that, in the absence of effective regulation, they will continue to make modified risk claims.

¹⁹ HHS, *Preventing Tobacco Use Among Youth and Young Adults, A Report of the Surgeon General*, 2012, at 539-541 and sources cited therein.

It is appropriate to consider all the foregoing elements in evaluating the sufficiency of the guidance.

II. The Statutory Standards

A. Definition of Modified Risk Tobacco Products and the Scope of the Decisions FDA Must Make under Section 911.

Section 911 defines a “modified risk tobacco product” 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.” Sec. 911(b)(1). The statute further defines such products to include a tobacco product, the label, labeling or advertising of which represents, explicitly or implicitly that

- (I) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
- (II) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
- (III) the tobacco product or its smoke does not contain or is free of a substance.

or

...the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product’s label, labeling, or advertising, after the date of enactment of the Tobacco Control Act, respecting the product that would be reasonably expected to result in consumers believing that the tobacco products or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of a substance or substances.

Sec. 911(b)(2)(A)

In addition, Section 911 defines “Modified Risk Tobacco Products” to include tobacco products “the label, labeling, or advertising of which uses the descriptors ‘light,’ ‘mild,’ or ‘low’ or similar descriptors” and prohibits tobacco product manufacturers from using such descriptors in labeling or advertising in the absence of the grant of an application under Section 911.²⁰

The Secretary is directed to grant an application to market a product as a “modified risk product” only if the Secretary determines that the applicant has demonstrated that such product, as it is actually used by consumers, will

- (A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

²⁰ The prohibition on the use of such descriptors in labeling or advertising was effective June 22, 2010. However, the prohibition on explicit or implicit health claims has been effective since June 22, 2009 and should apply to any statements since that date making such claims about cigarettes to be sold with color-coded pack designations subsequent to the effective date of the prohibition on explicit descriptors.

Sec. 911(g)(1)

This “public health” standard is similar to the standard set forth in other parts of the Tobacco Control Act, such as section 907 (authorizing FDA to set product standards) and section 910 (authorizing FDA to set standards for the marketing of new tobacco products). Significantly, this standard differs from the “safe and effective” standard applied by FDA with regard to the regulation of drugs and devices. The standard requires a product to meet two independent requirements: first, the product must “significantly reduce harm and the risk of tobacco-related disease to individual tobacco product users,” and second, even if the product meets this exacting standard, the FDA must find that permitting the product to be marketed as a modified risk product would “benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.” Sec. 911(g)(1) Furthermore, the burden is clearly on the applicant to demonstrate that both of these standards have been met.²¹

A tobacco product cannot be marketed without the prior grant of an application by the FDA if claims made about the product, either implicitly or explicitly, would reasonably be understood by consumers to mean that the product had a lower risk of harm or lower exposure to harmful constituents. This provision applies not only to products that may be marketed in the future but also to products that are currently marketed. With respect to such products, no claim may be made after June 22, 2009 without the prior grant of an application by FDA.

Several tobacco products currently marketed are or have been the subject of explicit or implicit modified risk claims, including products that have been and continue to be marketed as being “organic,” “all natural” or having “no additives” and products formerly marketed as “light” cigarettes sought to establish a program of color coding whereby such descriptors would be indicated by colors used in the packaging.

It is important for FDA to initiate enforcement actions promptly to ensure that tobacco products do not continue to be marketed in violation of the statutory standards.

B. Statutory requirements for submission of information

Section 911(d) establishes statutory standards for the information to be submitted in connection with an application for designation as a modified risk tobacco product. The information required to be submitted includes, *inter alia*, “all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health.” Sec. 911(d)(6) It also requires submission of “data and information on how consumers actually use the tobacco product.” Sec. 911(d)(7)

Section 911(d) also requires applicants to submit “such other information as the Secretary may require.” This section provides explicit authority for FDA to require the submission of any information necessary for it to determine whether the applicant has borne the burden of demonstrating that the statutory criteria have been met.

²¹ Section 911(g)(1) authorizes the Secretary to grant an application to market an MRTTP only if “*the applicant has demonstrated*” the required facts. (emphasis added)

C. Additional requirements for approval of an application

The statute also provides, *inter alia*, that any order authorizing the marketing of an MRTP may be effective only for a specified period of time. Sec. 911(h)(4). The statute also instructs the Secretary to require post-market surveillance and studies with respect to any MRTP. Sec. 911(i). The results of such surveillance and studies are to be submitted to the Secretary annually to enable the Secretary to evaluate whether the determinations on which the application was granted were and are still accurate. The Secretary is authorized to withdraw authorization if the applicant has failed to conduct or submit the required post-market surveillance and studies or failed to meet a condition of the order, or if any post-market surveillance or studies reveal that the order is no longer consistent with the protection of the public health. Sec. 911(j).

In addition, Section 911(h) requires any advertising or labeling concerning modified risk products to “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 of the diseases and health-related conditions associated with the use of tobacco products.” Furthermore, Section 911(h)(2) gives the Secretary authority to require specific additional comparative information for claims comparing a tobacco product to one or more other tobacco products.

The Secretary is also authorized to require disclosure on the label of other substances in the tobacco product or substances that may be produced by consumption of the product that may affect a disease or health-related condition or that may increase the risk of other diseases or health-related conditions associated with the use of tobacco products. In addition, the Secretary is authorized to require labeling of conditions of use if such conditions may affect the risk of the product to public health. Sec. 911(h)(3)

D. Statutory requirements for implementing regulations

The guidance at issue in this docket is intended to implement Section 911(l), which establishes specific parameters the guidance or regulation issued by the Secretary is to meet. These parameters include the following:

- (A) to the extent that adequate scientific evidence exists, the Secretary must establish minimum standards for scientific studies needed prior to issuing an order permitting the marketing of a modified risk tobacco product to show that a substantial reduction in morbidity and mortality among individual tobacco users occurs (for modified risk products) or is likely (for reduced exposure products);
- (B) include validated biomarkers, intermediate clinical endpoints, and other feasible outcome measures, as appropriate;
- (C) establish minimum standards for post-market 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 post-market surveillance, including ongoing assessments of consumer perception;

(E) require that data available from the required studies and surveillance be made available to the Secretary prior a decision on renewal; and

(F) establish a reasonable timetable for the Secretary to renew an application.

III. Comments on the Guidance

A. General Comments

1. Issuance of guidance rather than regulation

The statute requires FDA to issue “regulations or guidance (or any combination thereof) on the scientific evidence required for assessment and ongoing review of modified risk tobacco products not later than two years after the date of enactment.” FDA has chosen to issue guidance rather than regulations. To meet the statutory deadline, FDA’s decision to issue a guidance is understandable. However, once the guidance is finalized, FDA should establish such requirements as legally binding regulations at the earliest possible date. Maintaining the highest requirements for the integrity of the information submitted in connection with MRTP applications is a goal of primary importance. The tobacco industry’s record of deceit and duplicity in making health claims for tobacco products, its record of suppressing scientific evidence that might be contrary to its economic interest, and the financial incentives provided by approval of an MRTP application all provide strong reasons why requirements for the submission of scientific evidence should be established in regulations that are legally binding on the manufacturers. For example, a manufacturer that fails to disclose adverse scientific evidence regarding tests of a product should thereby become subject to legal action for violation of a regulatory requirement.

In a situation in which history demonstrates a substantial possibility that information adverse to the applicant may be withheld, the importance of establishing binding regulations is apparent.

2. Burden of providing evidence

The purpose of the proposed guidance is to inform manufacturers and the public about the evidence that will have to be submitted for FDA to consider an application to market a product as a modified risk tobacco product (“MRTP”). The statute makes clear that the burden of establishing each and every element for the grant of such an application is on the manufacturer. Although FDA is permitted to consider evidence from sources other than the manufacturer, the absence of sufficient evidence to establish any one element of the required standards will require rejection of the application. Although the statutory requirements and the language of the guidance are both premised on the principle that the manufacturer bears the burden of establishing the scientific evidentiary basis for each such element, we recommend that FDA make this principle explicit in the guidance.

3. Relationship of the guidance to the Institute of Medicine report

The report issued by the Institute of Medicine, “Scientific Standards for Studies on Modified Risk Tobacco Products,” provides a thorough, sound and thoughtful discussion of each element relevant to consideration of applications under Section 911.²² The scope of the Institute

²² Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December, 2011.

of Medicine report is somewhat broader than that of the guidance in that it addresses not only the evidence to be submitted by an applicant, but also criteria to be applied by FDA in evaluating such evidence. It therefore deals in considerably more detail with most of the statutory criteria. (For example, in discussing the relevance of various studies, the report deals at length with the way such studies should be designed in order to provide reliable evidence.)

In general, the guidance is consistent with the text and the recommendations of the Institute of Medicine report, but because the guidance deals only with the evidence to be submitted by manufacturers it does not include much of the detailed discussion in the Institute of Medicine report. We believe the guidance would be more informative to manufacturers and the general public if it incorporated even more extensively and more explicitly the discussion and, in particular, the recommendations of the Institute of Medicine report. In the comments that will follow, we will refer to the report and identify at least some of the areas in which the guidance could be improved by more explicitly incorporating discussion and recommendations from the Institute of Medicine report.

4. The importance of consumer perception

The guidance appropriately recognizes the central place of consumer perception in the evaluation of MRTP applications. The guidance recognizes that “FDA must ensure . . . that the advertising and labeling of the MRTP 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 of the tobacco-related diseases and health conditions.” (Part II, lines 171-75).

Recognition of this important principle means that the guidance must require extensive studies to establish what consumer perception of and behavioral reaction to given claims will be. To be explicit, studies must focus not only on the claim itself, but on what message consumers actually derive from the claim. For example, modified risk claims may be conveyed using numbers or percentages (i.e., presenting reductions in toxic constituents or claiming reductions in risk of certain diseases). We urge FDA to pay particular attention to ensuring that consumers understand the numbers used in conveying the reduced risk, the concept of risk itself, and the implications of such risk communications for their personal health. For example, if a claim is made that there is a given reduction (e.g., 10%) in cancer risk, consumer perception studies should be required to show that consumers have an accurate understanding of what such a reduction means. There is also a pressing need for studies to determine how best to communicate modified risk when reductions in a constituent, for example, do not correspond to a significant change in the associated health risks or alter risk of one disease, but not another. FDA should also consider how consumers will perceive and respond to modified risk claims that a product carries a lower risk for one tobacco-related disease, such as lung cancer, but continue to carry risk equal to other tobacco products for other tobacco-related diseases, such as cardiovascular disease.

Consumer perception may differ significantly in various population groups and the range of consumer perception studies presented by an applicant must yield evidence about consumer perception in all groups that will be exposed to the advertising and marketing of the product, with a heightened focus on the groups most vulnerable to modified risk claims.²³ Youth may be targeted for products geared to appeal to non-smokers. Marketing strategies for other products may target specific demographic groups.

²³ See discussion at 37-38 regarding studies of vulnerable populations.

In addition, consumer perception studies must be conducted both before the grant of an application and as part of post-market monitoring in order to determine how consumers actually understand modified risk messages after a product is marketed and to permit the FDA to respond to unanticipated reactions.

Moreover, because consumer understanding of modified risk claims may be affected by the context and surroundings in which they are made, studies must accurately reflect such context. Moreover, studies of consumer perception of claims must be done with reference to all relevant aspects of the claim. Many claims have both verbal and non-verbal messaging. For example, color coding has become an important way for tobacco companies to send non-verbal messages to consumers about alleged attributes of cigarettes. A claim presented on an advertisement that features a blue motif may give rise to consumer perception that differs from the same verbal message delivered in an advertisement that features a red motif.

Finally, FDA should consider whether the marketing of MRTPs using familiar brand names of conventional (i.e., non-MRTP) tobacco products creates the potential for consumer confusion. FDA should require provision of data on how the use of such brand names may affect consumer perceptions of both the MRTP and the non-MRTP product.

5. Consistency of MRTP review with FDA regulation of drugs with abuse potential.

The MRTP Draft Guidance emphasizes rigorous pre- and post-market review of MRTPs to determine their effects on individuals and the public health. This emphasis is consistent with FDA's increased focus on studying the risks associated with the use of the products it regulates (including approved products). In the drug area, this emphasis led Congress, as part of the FDA Amendments Act of 2007 (FDAAA), to authorize FDA to require Risk Evaluation and Mitigation Strategies (REMS) for approved drugs to ensure that the benefits of those drugs outweigh the risks. 21 USC 355-1. REMS are used, for instance, where a drug has high abuse potential, and its use therefore needs to be closely controlled and monitored.²⁴ As part of a REMS, FDA can require, among other things, manufacturers to adopt "elements to assure safe use" (ETASUs) of the approved product. 21 USC 355-1(f)(3). These ETASUs – which are appropriate when communications plans, package inserts and similar risk management measures are insufficient – can include, for example, measures to educate prescribers, dispensers, and patients; limited access programs aimed at ensuring appropriate, controlled uses of the products; and robust post-market surveillance and reporting. *Id.*

As one observer has noted, "[h]ow FDA deals with drugs having abuse potential may present a reasonable framework for MRTPs, as they share a common concern about use by persons other than the intended consumers"²⁵ – in the case of MRTPs, non-tobacco users or persons who use MRTPs to supplement their use of conventional tobacco products. The REMS example serves as both a guide and a counterfactual for the risk reduction strategies that are appropriate in the MRTP context.

²⁴ O'Connor, R. "Postmarketing Surveillance for 'Modified Risk Tobacco Products,'" 14 (1) *Nicotine and Tobacco Research* 29-42, 2012 (noting at p. 30 that "[o]ne class of drugs where REMS are likely to evolve in importance is those having abuse liability").

²⁵ *Id.*, p. 36.

First, as they are for REMS products, robust post-market surveillance regimes for MRTPs are essential in order for FDA to assess and reassess the risks of MRTPs to individuals and the public health. The MRTP Draft Guidance at pp. 29-33 emphasizes the need for aggressive post-market surveillance and review, and we agree that no MRTP should be approved unless the sponsor agrees to participate in such surveillance/review. We also urge FDA to consider whether it should adopt REMS or other specific risk management plans for approved MRTPs, along the lines of what has been adopted for approved drugs, where possible.²⁶

At the same time, it is important to recognize that MRTPs, unlike REMS products but like OTC NRTs, will be available without a prescription and therefore without physician or pharmacy intervention. Therefore, certain REMS procedures which are directed at or control the behavior of physicians and/or pharmacists, or limit access to supervised, monitored settings (21 USC 355-1(f)(3)(A)-(F)), would be unavailable in the MRTP context. This places a greater burden on FDA, and on the MRTP sponsor, to assess the risks of the MRTP *pre-market*.

6. What constitutes a claim?

No representation—either explicit or implicit—may be made that a product presents a lower risk of tobacco-related disease or exposure concerning risk or exposure unless FDA has first granted an application under Section 911. The potential coverage of section 911 extends to claims whether made explicitly or implicitly, verbally or non-verbally. Moreover, the coverage extends to actions directed to consumers that “would be reasonably expected to result in consumer beliefs” about the risk posed by tobacco products.” This language should cover a range of activities beyond the simple verbal statement of a claim.

7. Application of requirements to products that are currently marketed

Several tobacco products are currently being marketed that raise serious questions about whether they are or have been the subject of explicit or implicit modified risk claims in violation of Section 911. These include products that have been and continue to be marketed as being “all natural” or having “no additives” and, as noted above, products formerly marketed as “light” cigarettes and as to which explicit claims were made that sought to establish a program of color coding whereby such descriptors would be indicated by colors used in the packaging.

Although it is clear that the guidance applies to both products that are currently marketed and to products that have not yet been marketed, it is important for FDA to initiate enforcement actions promptly to ensure that tobacco products do not continue to be marketed in violation of the statutory standards.

The guidance correctly states that adding modified risk claims to the label or packaging of a tobacco product that is already marketed makes the product a new tobacco product. If such claims are made, an applicant would have to satisfy both the applicable premarket review requirements of section 910 and the requirements of section 911.

The breadth of this definition is particularly relevant in considering promotional materials distributed by the major tobacco companies in response to the prohibition on specific descriptors

²⁶ Ibid, p.30 (noting that FDA “needs vigorous systematic monitoring of MRTPs to minimize untoward population effects” and posing question, at 37, “[s]hould REMS or similar risk management plans be required for [MRTPs]?”)

for cigarettes. As noted above, the statute explicitly states that use of the descriptors “light,” “mild,” or “low” (or similar descriptors)—all of which were prohibited for cigarettes effective June 22, 2010—constitute modified risk claims. Moreover, the statute—and the guidance—make it clear that a claim is made if a tobacco product manufacturer “has taken any action directed to consumers through the media or otherwise, other than by means of a tobacco product’s label, labeling, or advertising, after June 22, 2009 “that would reasonably be expected to result in consumers believing that a tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products.” Section 911(b)(2) This statutory standard would prohibit any tobacco product manufacturer from taking any action after June 22, 2009 that would reasonably be expected to result in consumers believing, for example, that cigarettes packaged in blue packs and sold without the designation “light” were in fact the equivalent of cigarettes carrying the designation “light.” Thus, any actions taken by manufacturers subsequent to June 22, 2009 that could reasonably have been expected to have resulted in causing such a belief would constitute a violation of section 911.

As demonstrated supra at pages 11-12, several tobacco product manufacturers did, after the date of enactment of the Tobacco Control Act, circulate materials with the intention of communicating to consumers directly and through retailers that cigarettes with certain pack coloring or configuration sold after June 22, 2010, the date on which the prohibition on descriptors went into effect, presented a lower risk of disease or were less harmful.²⁷ The effect of such actions is to help perpetuate the erroneous belief that cigarettes sold with certain colors and packaging carry a reduced risk of disease or exposure to the individual smoker. Making such claims falls squarely within the category of conduct that Section 911 was designed to prohibit. We call upon FDA to take appropriate regulatory action to remedy the consequences of this violation and to punish this willful violation of law.

8. Relationship between New Product Applications under Section 910 and Modified Risk Applications under Section 911.

The requirements for issuance of an order under Section 910 permitting the marketing of a new tobacco product are distinct from the requirements for issuance of an order under Section 911 permitting the marketing of a product as a modified risk tobacco product. The requirements of Section 910 deal with the product itself, whereas, the requirements of Section 911 deal with claims made about the product, either explicitly or implicitly.

B. Specific Comments

1. Claims made in testing to support an application

The statute prohibits the introduction into commerce of products as to which a modified risk or modified exposure claim is made in the absence of an order issued by the FDA permitting such a claim under Section 911. A product about which no such claim is made may be marketed commercially if it otherwise meets regulatory requirements so long as no modified risk or modified exposure claim is made.

It is apparently not FDA’s intention to prohibit such claims for products that are the subject of testing to establish whether they meet the requirements of section 911. Appropriate

²⁷ See Appendix A.

limits should be established to ensure that claims made in this limited context are not disseminated more broadly than necessary to ensure the integrity of the test.

2. Description of the proposed tobacco product

The guidance calls for submission of information about, inter alia, all components and a description of all design features, including ventilation holes, heat source, paper porosity, coatings, and nicotine concentration gradient). Inclusion of all such design features is essential to effective regulation. Such design features can substantially change the delivery of smoke constituents, including nicotine, toxicants, and carcinogens. Understanding precisely the design features of the product is indispensable in any analysis of the health effects of its use.

The guidance also calls for information concerning the handling or storage of the product. Handling and storage can change the characteristics of a product in ways that affect the delivery of smoke constituents. Thus, such information is directly relevant to FDA's concerns. The breadth of the proposed guidance is entirely appropriate.

3. Requirement of prior authorization for all draft promotional materials.

The guidance directs manufacturers to submit “copies of any draft promotional materials (e.g., advertising and labeling) developed by the time of the filing that the applicant expects will be used in marketing the MRTTP.” Because promotional materials affect consumer perception and consumer perception affects consumer behavior, close examination of all such materials by the FDA is essential prior to the issuance of an order authorizing any claim. The guidance, however, should go farther. Precisely because promotional materials have such a profound effect on consumer behavior, it is essential that any such materials be subject to review by FDA prior to their use and that they not be used without the issuance of an order authorizing such use. This condition applies as much to materials developed after the date of the application—or after the date an order is issued—as it does to materials developed before. The guidance should be amended to make it clear that no advertising or promotional materials that make a modified risk or modified exposure claim may be used, even after a modified risk order has been issued, unless FDA has reviewed and issued an order with regard to the particular advertising or promotional materials sought to be used. Any order granting an application under Section 911 should explicitly require such submissions.

The guidance properly requires an applicant to describe how it intends to communicate the proposed modified risk claim(s) to consumers, “including any actions directed to consumers that the [applicant] plans to take to communicate the proposed modified risk claims to consumers (other than by means of the product label, labeling, or advertising.)” This requirement is necessary to implement Section 911(b)(2)(A)(iii), which prohibits a manufacturer from taking any such action without an order from the FDA granting an application. As with advertising and promotional materials, however, the obligation to submit such statements to the FDA should expressly be made applicable to any such plans to communicate such claims at any time subsequent to the submission of the application, including any time subsequent to the issuance of an order. Any order granting an application under Section 911 should explicitly require submission of such statements.

4. Requirement of public availability and public participation

The statute requires that all applications made under Section 911 be made publicly available (except for matters in the application which are trade secrets or otherwise confidential, commercial information). Section 911(e)

Furthermore, Section 911(e) requires FDA to “request comments by interested persons on the information contained in the application and on the label, labeling, and advertising accompanying such applications.” Sec. 911(e) The statute thus clearly contemplates public participation in the consideration by FDA of any such application. In order to make such public participation meaningful, FDA must adopt a definition of what constitutes “trade secrets or otherwise confidential, commercial information” that is not so broad as to prevent potential public participants from providing meaningful input in the decision-making process. By withholding essential elements of an application, meaningful public participation could be precluded. This result would be contrary to the clear statutory direction. In no event should the content of any proposed advertisement be deemed to be exempt from required public disclosure during the application process under Section 911(e). In the context of Section 911, a marketing strategy cannot be deemed to be a trade secret or confidential commercial information. The pervasive use of legal subterfuges by the major tobacco companies to avoid disclosure of information was extensively documented in *U.S. v. Philip Morris*.²⁸ Provisions should be incorporated in guidance and regulations to prevent such conduct.

5. Conditions for using the tobacco product

As required by Section 911 (d)(2), the guidance requires submission of information regarding the conditions for using the product. The way in which a consumer consumes the product is extremely important in evaluating the level of delivery of toxicants and other harmful constituents. For example, as demonstrated elsewhere, the conditions under which cigarettes labeled “light” were actually used by consumers differed substantially from conditions under which cigarettes were smoked by machines and consequently the expected yields of various constituents as actually experienced by consumers differed greatly from machine-measured yields. Moreover, the manner in which consumers smoked—including covering ventilation holes in the filters—greatly affected the outcome.²⁹ Thus, gathering of comprehensive information on conditions of use is important. The information sought by FDA is essential to address these legitimate concerns. Included in the conditions to be assessed is also the amount and frequency with which a consumer uses the product compared to the consumer’s current use of tobacco products.

6. Formulation of the tobacco product

As required by Section 911(d)(3), the guidance requires submission regarding the formulation of the product. Provision of information regarding each of the elements specified in the guidance is necessary for a proper analysis in accordance with the statutory purpose. The guidance calls for a complete list of uniquely identified components, ingredients, and additives by

²⁸ *U.S. v. Philip Morris*, *supra*, note 3. 449F. Supp. 2d. at 832-839.

²⁹ National Cancer Institute, *Risks Associated with Smoking Cigarettes with Low Tar Machine-Measured Yields of Tar and Nicotine*, Smoking and Tobacco Control Monograph No. 13, November, 2001. See also, National Cancer Institute, *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes*, Smoking and Tobacco Control Monograph No. 7, August, 1996.

quantity. Requiring this information for all such components, ingredients, and additives for modified risk products is appropriate. In the Guidance issued contemporaneously regarding submission of information on hazardous and potentially hazardous constituents, FDA suggests that under Section 904, on an interim basis, information could be provided for only twenty out of 93 separately identified constituents. Regardless of whether such a limitation is appropriate under the statutory provisions governing that guidance (section 904), no such limitation is appropriate with regard to a modified risk tobacco product application. Components that impact who smokes, how much one smokes, who starts and who quits are directly relevant. A manufacturer applying for an order that would permit it to market a product as modified risk must provide comprehensive information on all components, ingredients, additives—and constituents—in the product. The guidance should be made more explicit with regard to this requirement. Moreover, smoke constituents must be included in the list of substances about which quantitative information must be supplied.

The guidance correctly requires submission of information on tobacco, paper, glue, flavorings, burn-rate controllers, and pH modifiers because all these elements can affect the delivery of harmful substances to the consumer as the product is actually used. In addition to these elements, the filter and its components should be specifically identified, even though the language of the guidance is sufficiently broad to include it.

The guidance correctly requires submission of information regarding tobacco blending, reconstitution, or manipulation because each of these activities can affect the delivery of harmful substances to the consumer as the product is actually used. For the same reason, provision of the requested information regarding manufacturing steps is relevant and important, as is provision of a description of how the design, materials, ingredients, and heating source combine to produce the final product.

Provision of a quantitative description of performance criteria is also important. The guidance should also require provision of information demonstrating the degree to which products introduced into commerce conform to such criteria. A manufacturer that is not capable of achieving a high degree of consistent quality control should not be permitted to make modified risk claims about its product. This requirement should be made explicit in the guidance and requirements to confirm that continued quality control is an appropriate subject for postmarket surveillance.

Finally, the provision in the guidance requiring the submission of data establishing the stability of the product through the stated shelf life is also essential to FDA's consideration of the product because changes in the product could affect the delivery of substances to consumers.

7. All documents relating to research findings

Section 911(d)(5) of the statute contains provisions requiring submission of all documents relating to research findings. The guidance appropriately adopts the language of the statute, which clearly requires submission of *all* such documents, whether favorable or unfavorable. Moreover, the guidance appropriately includes the provision to require documents regarding such research whether or not the research or studies were conducted or supported by the manufacturer. Such information must be provided so long as the manufacturer has received or is aware of the information to inform the development of the product.

FDA should also specify that the tobacco manufacturers are obligated to provide information from studies conducted on other products as well as research conducted prior to the

date of enactment of the FSPTCA that in any way relates to any of the ingredients or constituents or in any way could be considered to be relevant to FDA's assessment of any of the criteria set forth in Section 911.

In evaluating the sufficiency of the guidance in this respect, it is important for FDA to be aware of the long history of misconduct by tobacco companies in finding ways to avoid production of documents that they deemed contrary to their financial interest.³⁰ The evidence shows that documents were placed in the custody of outside law firms or were stored outside the United States in order to avoid having to disclose their contents.³¹ FDA must make such action a violation of its rules punishable to law. The need for such a requirement illustrates why, it is particularly important for FDA to issue regulations that are binding on the applicant.

8. Data on how consumers actually use the tobacco product

The statute requires FDA to take account of the potential effect of an order permitting the marketing of an MRTP as the product is actually used by consumers. Section 911(d)(6). Accordingly, the guidance properly requires provision of information and evidence on whether consumers are likely to comply with instructions for product use, the number of units consumed per day, smoking topography, and concurrent use. All these factors have a potential impact on the delivery of toxicants and addictive constituents and therefore on the health effects of the product and population impact of any claims. It is essential that FDA receive data on actual human exposure when the product is used under normal conditions and require the manufacturer to provide that data as part of the review process and as part of the post market surveillance process.

The regulatory experience with light cigarettes is again instructive regarding the importance of focusing on how consumers actually use the product. In that case regulatory policy was developed on the assumption that yields of constituents measured from smoking machines was an appropriate measure of constituent yields that would be experienced by consumers. In fact, however, a variety of circumstances caused those yields to differ materially from actual yields experienced by smokers and a misguided and counter-productive policy was implemented—with disastrous public health consequences.

There is overwhelming evidence that the major tobacco companies were aware that the policies that had been adopted were based on erroneous data long before public health officials were aware of this fact. They were also aware of the population impact of being able to label these products as “Light” or “Low Tar.” Rather than coming forward with this information, the companies concealed it and continued to spend billions of dollars making health claims for cigarettes they knew were no safer—claims they knew were persuading many smokers not to quit smoking.³²

The lesson to be drawn from this experience is not only that constituent yields need to be measured in accordance with the way consumers actually use the product, but that tobacco product manufacturers cannot be trusted to come forward with information regarding the public

³⁰ U.S. v. Philip Morris, 449 F. Supp. 2d. at 801-832.

³¹ *Id.*

³² U.S. v. Philip Morris, 449 F. Supp. 2d. at 430-431.

health consequences of using their products if they regard that information as contrary to their financial interest and that, absent effective regulatory action, they will continue to sell and promote those products regardless of the public health consequences of doing so. Accordingly, provisions requiring production of information need to be drawn clearly and explicitly. Furthermore, particularly in light of the extensive factual findings in *U.S. v. Philip Morris* regarding the falsification and suppression of scientific data by the major tobacco companies, FDA should not accept proffered industry data at face value as complete or accurate. FDA should ensure that disclosure requirements are complete and strong enough to permit FDA to undertake its own independent assessment of the validity of protocols and statistical analysis of the submitted results.

9. Provision of Other Information

The guidance gives several examples of information FDA may request. Two of these elements—listed in the fourth and fifth bullet points—should be part of required disclosure. These two elements are, for products that have been on the market prior to the MRTP submission, data on adverse events,³³ levels of product use and consumer feedback and, for products that have not been on the market prior to the submission, a summary of market research and information used to inform the development of the new product and its label, labeling and market plan. Given the harm caused by tobacco products, it is also necessary for FDA to specify what it considers an “adverse event”. The definition should not be limited to extraordinary events, such as contamination, but should include data on regularly occurring events resulting from tobacco use. Provision of all such information is relevant in making determinations both about the impact of the product on individual consumers and about its impact on the public health at the population level. Information about market research and product development is of prime importance in evaluating consumer perception that will result from the marketing of the product. It is important that production of this information be made part of the disclosure required when an application is filed.

The guidance also states that if a manufacturer becomes aware of any new information relating to the effect of the proposed product on tobacco-related diseases and health related conditions while an application is pending, the manufacturer should promptly provide this information to FDA. Such action should be required by a binding regulation, not merely encouraged in the guidance. Moreover, failure to comply with this requirement should result in sanctions of sufficient seriousness to compel compliance. Moreover, this requirement should not be limited to information that comes to the attention of the manufacturer while an application is pending, but at any time—including after an application has been granted.

IV. Scientific Studies and Analysis in MRTPAs

The guidance lists five key areas of investigation. Each of these areas is appropriately designated and is linked to the standard FDA is directed by the statute to apply in considering the application. Examination of evidence in each of these categories is necessary for FDA to conduct the required review. The requirements for disclosure are too limited to ensure that a tobacco company could not present information in a misleading way. The requirements should be strengthened to prevent such actions.

³³ The magnitude of the harm resulting from the usage of tobacco products dwarfs any conceivable adverse effect in the history of drug regulation.

A. Health Risks of the Tobacco Product

The guidance apparently uses the term “health risks of the tobacco product” to refer to “the risk of tobacco-related disease to individual tobacco users” as that term is used in Section 911(g)(1)(A).

1. Product analyses

a. Constituents tested

The guidance requires submission of information regarding “product analyses to validate information provided by the applicant regarding the formulation of the product as it relates to the risk or exposure modification” and “to assess users’ and non-users’ potential exposure to harmful substances.” (lines 677-80)

The guidance states that for each product FDA recommends applicants conduct product analyses to determine the levels of harmful and potentially harmful constituents (HPHC) including smoke constituents, “as appropriate to the product.” Applicants are advised to “test for and report on the HPHC list as established by FDA under Section 904(d).”

As noted above, FDA has established a list of HPHC containing 93 such constituents. The guidance should state explicitly that product analyses to support a MRTPA should include submission of data on every one of those 93 constituents even if such information is not required under Section 904. Under the proposed guidance on HPHC, FDA calls for prompt submission of data on 20 of those 93 constituents and defers imposition of reporting data on the other 73.³⁴ Regardless of the reasons for that deferral, this guidance should make it clear that submission of data for every one of the 93 constituents is required for an MRTPA. No product should be permitted to be marketed with a modified risk or a modified exposure claim unless information has been submitted and fully evaluated on every constituent identified as harmful or potentially harmful.³⁵

Moreover, FDA indicated that its initial list of 93 constituents is restricted to those constituents found to contribute to the development of only a few of the many tobacco-related diseases and further that the list is restricted to those constituents previously designated as harmful or potentially harmful by other national or international bodies.³⁶ Thus, the list will need to be expanded in the future. The guidance should establish a requirement that any MRTPA should include product analysis data with regard to all constituents listed on any such expanded list. Moreover, the guidance should require that when an additional constituent is added to the list compiled pursuant to section 904, every existing manufacturer of an MRTP must submit

³⁴ FDA, Center for Tobacco Products, FDA, Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, March 2012.

<http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm297741.htm>

³⁵ The same requirements should apply with regard to substantial equivalence and new product applications.

³⁶ FDA, Center for Tobacco Products, FDA, Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, March 2012.

supplemental data with regard to such constituent as a condition of continuing to market such product.

For FDA to comply with the requirements of Section 911, it must also require data beyond those constituents categorized as harmful or potentially harmful. Ingredients and constituents that increase the addictiveness and appeal of a product also are critical components of a Section 911 analysis. The Guidance should require tobacco manufacturers to provide information about any ingredient or constituent that could potentially impact addictiveness or appeal and provide the FDA with the flexibility to require that information for any ingredient or constituent that it considers appropriate for this purpose.

Machine testing

The guidance requires applicants to determine quantitative levels of constituents using both ISO and Canadian Intense smoking regimens. Despite the limitations of machine testing noted elsewhere in these comments, information developed in machine testing is relevant to (but not determinative of) the evaluation of the potential effects of a product on an individual's health. Thus, machine testing is an appropriate requirement; however, the results of machine testing alone will never be adequate to comply with the requirements of Section 911. Based on currently available data, the requirement to provide these two types of test results is warranted. FDA should explicitly reserve the right to alter the tests required as new evidence becomes available.

2. Sequencing of scientific studies

One of the most important recommendations of the Institute of Medicine report was the recommendation that scientific studies be sequenced so that clinical studies on human subjects would not be undertaken until after FDA had evaluated comprehensive information from preclinical studies and determined that there was sufficient likelihood of positive results to justify human studies. This recommendation is important because the clinical tests of lethal products on human subjects raise serious ethical issues and should not be undertaken without strong justification. For example, such studies could involve the effect of potentially misleading claims on use behavior. Moreover, in testing involving consumer perception of claims there is a danger that individuals outside the circle of intended subjects could be exposed to the claims. The potential adverse effects of unnecessary human testing should be minimized.

3. Human studies

The guidance calls for submission of human studies regarding actual use of the product to determine if users are likely to use the product in a manner that reduces their individual health risks or exposures compared to using other tobacco products and to show that use of the product will result in a significant reduction of harm and the risk of tobacco-related disease to individual users. These areas of inquiry are designated as criteria for determining if a product qualifies for designation as an MRTP in Section 911(g). The requirement for human testing to make this determination is an absolutely critical requirement.

4. Nonclinical or human studies

The guidance calls for submission of nonclinical and/or human studies to demonstrate that the substances or exposures that have been reduced are harmful and to demonstrate that use of the product is expected to result in "a measurable and substantial reduction in morbidity or mortality to individual tobacco users based on the effects of the product on an endpoint that is

reasonably likely, based on epidemiological, therapeutic, pathophysiologic, or other evidence, to predict an effect on reducing harm or disease.” (lines 696-701) The requirement for these showings is contained in the statute and the designation of the kinds of studies that may be submitted to meet them is a reasonable one.

5. Benchmarks for comparison

Importantly, the guidance recommends that scientific studies regarding the risk of the product should enable FDA to fully assess the product according to six specified benchmarks:

- The health risks associated with the use of the product as compared to using other tobacco products on the market;
- The changes in health risks to users who switch from using another tobacco product to using the product;
- The health risks associated with switching to the product as compared to quitting the use of tobacco products;
- The health risks associated with using the product in conjunction with other tobacco products;
- The health risks associated with switching to the product as compared to using an FDA-approved tobacco cessation medication; and
- The health risks associated with initiating use of the product as compared to never using tobacco products.

These benchmarks are derived from standards stated in the statute and they represent the most important points of comparison for consideration of an MRTPA. The first five relate to evaluation of health risks to existing tobacco users, while the sixth relates to evaluation of health risks to non-users.

It is essential for evidence to be presented addressing each of these comparisons. Because the health risks associated with switching to the product as compared to using an FDA-approved tobacco cessation medication involve a parallel set of regulatory criteria, we have included a separate and more extensive discussion at section IV C (at pp. 37-40). We believe that it would be beneficial for FDA to consider regulatory criteria regarding tobacco cessation medication to be evaluated at the same time and in the light of its consideration of this guidance. Moreover, we believe that adoption of an overall policy on modified risk products requires a re-examination of FDA’s policy regarding tobacco cessation medication.

With regard to health risks presented to non-users, we suggest that two additional areas be examined: (1) health risks associated with the use of the product as a gateway to using other tobacco products and (2) health risks to those who have quit using tobacco products and may resume by using the product. There is considerable evidence that certain tobacco products are more acceptable to individuals who are initiating tobacco use than other tobacco products (e.g., low-nicotine vs. high-nicotine products). The promotion of such products to non-users as gateways to the use of other tobacco products is a serious concern. Moreover, a large portion of the most susceptible group of non-users is underage and the use of such products to initiate

underage users is a major potential problem. The potential for such effects was extensively documented in the most recent report of the Surgeon General.³⁷

In evaluating the effects on both individual and population-level health, it is relevant to consider the extent to which initiation of the use of low-nicotine modified risk products is likely to lead to use of conventional tobacco products. It should not be assumed that non-users who may initiate use with a modified risk or modified exposure product will limit their long-term use to that product.

It is also important to examine the likelihood that introduction of modified risk or modified exposure products will lead those who have quit using tobacco products to resume their use. In this connection as well, it is necessary to consider whether the resumption of tobacco use would be limited to use of the modified risk product or whether the use of such a product was a gateway to resumption of the use of conventional products.

B. Effect on the Health of the Population as a Whole

In evaluating the effect of an order permitting modified risk or modified exposure claims, the effect on the health of the population as a whole should be considered with regard to each of the benchmark categories enumerated in the preceding section.

1. Effect on tobacco use behavior among current tobacco users

One critical area for consideration is the effect an MRTP may have on tobacco use behavior among current tobacco users. The guidance correctly states that an application must “provide evidence regarding whether the product and its marketing will increase or decrease the likelihood that existing users of tobacco product who would otherwise stop using such products would instead switch to the tobacco product that is the subject of the application.” (p. 19, l. 735-39)

The guidance identifies relevant studies as:

Nonclinical and/or human studies to assess abuse liability and potential for misuse as compared to other tobacco products; and

Human studies regarding actual use and consumer perception of the product, including labeling, marketing, and advertising.

The guidance states that such studies should address the likelihood that current users will start using the product; switch to or switch back to other tobacco products with higher levels of individual risk; use the product in conjunction with other tobacco products; or use the product as intended. The guidance also states that the studies should address whether users who have quit would use the product. Each of these areas is relevant and important.

The guidance should also expressly focus on the potential for dual use (i.e., the use of an MRTP in conjunction with conventional tobacco products.) There is evidence that dual use of conventional tobacco products and smokeless tobacco products is increasing. All the major

³⁷ HHS, *Preventing Tobacco Use among Youth and Young Adults, A Report of the Surgeon General*, 2012.

tobacco companies have made significant investments in smokeless tobacco³⁸ and much of the advertising for smokeless products appears to be promoting dual use with messages like “Fits Alongside Your Smokes.”³⁹ Even among adolescents, a recent study found a greater probability of Snus use among those who reported current cigarette and cigar smoking and current use of smokeless tobacco (specifically chew).⁴⁰ The increasing prevalence of smoke-free laws has led to the promotion of smokeless products as alternatives to abstinence in situations in which it is not possible to smoke.⁴¹ In such situations, MRTPs may discourage cessation and there is the possibility that dual use will be more dangerous than the separate uses of the different products. It is important to require applicants to submit studies addressing the potential for dual use and the degree to which the grant of an MRTP application could discourage cessation or increase risk beyond the use of either product alone.

2. Effect on tobacco use initiation among non-users

The statute directs FDA to consider the effect of an MRTP on use initiation among non-users. Sec. 911(g)(1)(B) The large majority of such non-users are adolescents. In recent years, total sales of smokeless products have increased.⁴² One study showed that more young adults tried Snus compared to older adults.⁴³ A study using data from the 2009 Texas Youth Tobacco Survey showed that 7.1% of adolescents surveyed tried Snus and 3.9% of adolescent nonsmokers surveyed tried Snus.⁴⁴ In evaluating the effect of MRTPs on non-users, it is extremely important for FDA to have data that can demonstrate as accurately as possible whether the grant of an

³⁸ Federal Trade Commission, *Smokeless Tobacco Report for 2007 and 2008*, 2011, <http://www.ftc.gov/os/2011/07/110729smokelesstobaccoreport.pdf>.

³⁹ Carpenter C.M., et al., “Developing smokeless tobacco products for smokers: an examination of tobacco industry documents,” *Tobacco Control*, vol. 18, no. 1, pp. 54–59, 2009. Marlboro Snus, “Trinkets and trash: artifacts of the tobacco epidemic,” 2009, <http://www.trinketsandtrash.org/tearsheet.asp?ItemNum=212750>.

⁴⁰ Loukas A., et al. “Who uses snus? A study of Texas adolescents,” *Nicotine Tob Res.* 14(5):626-630, May 2012.

⁴¹ R.J. Reynolds Tobacco Co., Camel Snus advertisement stating, “NYC Smokers rise above the ban” in Village Voice, June 8, 2011. Courtesy of trinketsandtrash.org. Available at: <http://www.trinketsandtrash.org/tearsheet.asp?ItemNum=213303>; R.J. Reynolds Tobacco Co., Camel Snus advertisement stating, “Smokers, Enjoy first-class flavor” in the US Airways magazine, October 2011. Courtesy of trinketsandtrash.org. Available at: <http://www.trinketsandtrash.org/tearsheet.asp?ItemNum=213568>; R.J. Reynolds Tobacco Co., Camel Snus advertisement stating, “2012 Smoke-free REsolution” [emphasis in advertisement] in the Boise Weekly, December 21, 2011, Village Voice, December 28, 2011, QNotes (North Carolina), December 24, 2011, among other dates. Courtesy of trinketsandtrash.org. Available at: <http://www.trinketsandtrash.org/tearsheet.asp?ItemNum=213601>.

⁴² Federal Trade Commission. *Smokeless Tobacco Report for 2007 and 2008*. Washington, DC: Federal Trade Commission; 2011.

⁴³ Biener L, McCausland K, Curry L, Cullen J. Prevalence of trial of snus products among adult smokers. *American Journal of Public Health*. Oct 2011;101(10):1874-1876.

⁴⁴ Loukas A, Batanova MD, Velazquez CE, et al. Who uses snus? A study of Texas adolescents. *Nicotine Tob Res*. May 2012;14(5):626-630.

MRTP application will cause adolescents who would not otherwise have initiated tobacco use to do so. As the guidance indicates, submission of consumer perception studies involving adolescents is an essential element. Requiring such studies is particularly important given the industry's documented history of marketing lethal products to adolescents.⁴⁵

The guidance directs applicants to have their studies address initiation by those who have never used tobacco products; the likelihood that non-users who start using the MRTP product will later switch to other, higher-risk tobacco products; and the likelihood that those who have quit using tobacco products would reinitiate use with the MRTP product. The guidance identifies as relevant human studies that evaluate consumer perception of the product, including its labeling, marketing and advertising. Such studies are clearly required.

Moreover, in considering the effect of an MRTP on non-users, FDA should also consider the potential for the use of MRTPs as gateway products. Such products, which may be acceptable and attractive to non-users, may lead such new users to convert to the use of conventional tobacco products. The potential for such use should be evaluated both prospectively, when an application is made and, importantly, as an aspect of post-market analysis for any product as to which an application has been granted.

Another concern that should be part of the evaluation relates to product confusion. A great deal of the marketing of current smokeless tobacco products focuses on products the tobacco industry claims have lower levels of nitrosamines and heavy metals. Nonetheless, the largest increase in smokeless tobacco sales has been among traditional smokeless tobacco products with higher levels of nitrosamines and heavy metals. Thus, it appears that the claims for one type of smokeless tobacco product may cause consumers to believe, erroneously, that other types of products have the same characteristics. It is essential for FDA to require tobacco manufacturers to provide data to demonstrate that this type of product confusion will not occur.

3. Effect on former users

In considering the effect of an MRTP on non-users, FDA should also seek data on the effect of an MRTP on former tobacco product users who, faced with the prospect of a modified risk product, might consider resuming tobacco use. To the extent that an MRTP encourages a lapse in cessation, its effect on the public health is detrimental.

4. Effects of secondhand smoke

Information submitted in connection with an MRTP application should also include data on the effect of an MRTP on non-users who are exposed to secondhand smoke or who may otherwise be affected by another person's use of the product.

5. Effect of marketing on consumer understanding and perceptions

⁴⁵ Report of the Surgeon General (2012), 530-41, 603-27 and sources cited therein; U.S. v. Philip Morris, 449 F. Supp. 2d at 561-691.

The guidance properly recognizes that the effect of MRTPs and their marketing is an important consideration. The guidance states that MRTPAs must contain evidence to show that the advertising and labeling 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 of all diseases and conditions associated with tobacco use.

The guidance states that human studies regarding consumer understanding are recommended and suggests that studies should address: consumers' ability to understand the claim in the context of one's health; consumer beliefs about the health risks of the product relative to other consumer products, relative to cessation aids, and relative to quitting all tobacco use. Such studies are more than recommended; the Guidance should make it clear that such studies are required.

These areas are all appropriate. However, the guidance should also require studies to be submitted regarding consumer understanding among high-risk populations (i.e., populations that are either likely to be disproportionately vulnerable to misperception or disproportionately affected by the marketing of the product). Such groups would include adolescents,⁴⁶ those with mental or psychological conditions that render them particularly vulnerable to addiction, and any other demographic group that might be expected to be disproportionately at risk in the marketing of a particular product based on market history or marketing strategies. The Institute of Medicine report specifically recommended that studies be required for groups that are either particularly vulnerable or particularly likely to be targeted for a specific product, including "those in low socioeconomic status and educational attainment, and certain ethnic minorities."⁴⁷ The same considerations would require studies targeted to measure consumer perception in other groups with a disproportionately high incidence of tobacco usage, such as the LGBT community.⁴⁸ Moreover, the requirements for sampling should focus on demographic groups likely to be disproportionately affected by the particular claim. For example, weight loss claims should require sampling of women and particularly of adolescent women. FDA should amend the guidance to follow these recommendations.

6. Effect on the population as a whole

The statute requires applicants seeking an MRTP order to "demonstrate that [the] product, as actually used by consumers will benefit the health of the population as a whole taking

⁴⁶ *Id.*

⁴⁷ Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011 Recommendation no. 6, at 16-17.

⁴⁸ A growing body of evidence indicates that LGBT adults and youth are considerably more likely to use tobacco than the general population, with some studies estimating smoking rates as much as double the national average. *Tobacco Use Among Sexual Minorities in the USA, 1987 to May 2007: A Systematic Review*. Lee, JG, Griffin, GK, and Melvin, CL. 2009, Tobacco Control, Vol. 18, pp. 275-282; *Smoking Out A Deadly Threat: Tobacco Use in the LGBT Community*. American Lung Association, 2010. Available at <http://www.lung.org/assets/documents/publications/lung-disease-data/lgbt-report.pdf>. It is no surprise that the tobacco industry was one of the first to develop marketing materials specifically targeting the LGBT community. *An Analysis of Tobacco Industry Marketing to Lesbian, Gay, Bisexual, and Transgender (LGBT) Populations: Strategies for Mainstream Tobacco Control and Prevention*. Stevens P, et al. 2004, Health Promotion Practice, Supplement to Vol. 5(3); *Smoking Out A Deadly Threat: Tobacco Use in the LGBT Community* at pp. 11-12.

account both of users of tobacco products and persons who do not currently use tobacco products.” FDA appropriately recommends that applicants submit studies that show “quantitative estimates of the effect of the marketing of the product, as proposed, on the health of the population as a whole.” (p. 21, l. 838-39)

The guidance recommends that the estimates should integrate all of the information regarding the marketing of the product and its potential effects on health, tobacco use behavior and use initiation. The guidance recommends that the applicant include estimates geared to several different categories of potentially affected segments of the population. The guidance provides an illustrative example.

In addition to the groups specified in the guidance, we recommend the addition of groups who, either by virtue of their vulnerability or for any other reason, are likely to be affected disproportionately by the marketing of the product. Such groups should include, inter alia, persons with psychological or emotional disorders that have been associated with tobacco usage at levels significantly higher than those prevailing in the population as a whole.

C. Consideration of MRTPs in relation to the standards governing FDA’s regulation of smoking cessation products, including nicotine replacement therapies (NRTs).

MRTPs are promoted as a way of reducing the harms associated with the use of conventional cigarettes. These products are not free of the harm associated with tobacco use. They present *modified* risks, not *no risk at all*. Yet there are products already on the market that FDA has already deemed, after an extensive review process, to be safe and effective in treating nicotine dependence that do not carry the risks associated with tobacco use. These are so-called “smoking cessation” products or “tobacco dependence” products, including Nicotine Replacement Therapies (NRTs). Section 911(c) states that tobacco dependence products are not MRTPs if they have been approved as a drug or device by the FDA pursuant to Chapter V of the Food Drug and Cosmetic Act.

Some smoking cessation products do not contain nicotine, while NRTs “supply [the user] with nicotine in controlled amounts while sparing [him/her] from other chemicals found in tobacco products.” See “FDA 101: Smoking Cessation Products,” FDA Consumer Health Information (Jan. 2010) (“FDA 101”), available at www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM198176.htm. These products – which take the form of gums, patches, lozenges, and sprays – have been approved by FDA under the rigorous review standards the Agency applies to new drugs and medical devices under the Food Drug and Cosmetic Act. While some smoking cessation products are prescription-only, NRTs are generally available over-the-counter (OTC), but only after FDA has carefully reviewed the risks of making them available without a prescription.⁴⁹

The presence on the market of FDA-approved smoking cessation products, including NRTs, has three significant implications for the Agency’s regulation of MRTPs.

⁴⁹ In most cases, FDA first approved the NRT as Rx only and then approved an Rx to OTC switch. *Id.* at 16-18 (describing data supporting Rx to OTC switch for certain NRTs). Nicotine lozenges are the exception, having been approved initially for OTC use. *Id.* at 13-15 (detailing data supporting initial OTC approval).

First, the availability of safe and effective, FDA-approved smoking cessation products raises the threshold question of the role of MRTs and should be taken account of in evaluating an application for an MRTP. MRTPs. NRT products, by definition, have already been found to be both safe and effective and the language of any claims regarding their safety, efficacy and method of use has been specifically approved by the FDA. By contrast, MRTPs are not safe. Moreover, unless they meet all the same stringent tests as NRT products and are subjected to review by CDER, they cannot be promoted as smoking cessation devices. The marketing of MRTPs confers no benefit if consumers who would otherwise use NRT products instead use MRTPs. MRTPs confer a benefit only if those existing smokers who might use MRTPs instead would not quit or would not use NRTs. The Draft Guidance, at p. 4, notes that one measure of the risks and benefits of MRTPs ought to be “the risks and benefits to persons from the use of the [MRTP] *compared to* the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence.”

If MRTPs present greater risks and/or fewer benefits than FDA-approved smoking cessation products, these products do not advance the public health when they divert consumers away existing, available, safe and effective, FDA-approved therapies.⁵⁰ (emphasizing that “[i]f an MRTP has promise to attract individuals away from use of conventional tobacco products, it should be somewhat *more reinforcing* than NRT, promoting *greater sustained use* and substituting for conventional use *more effectively* than NRT” and that “[p]resumably, an MRTP would achieve meaningful use *only* if it were *more* appealing than NRT.”) (Emphasis added). The burden is, and should be, on the MRTP sponsor to demonstrate why its product *at least* confers a net benefit over and above what is already offered by existing FDA-approved therapies. *See* IOM Report at 184 (noting that an MRTP might not need to be “better than” an NRT “*if its modest effects were additive, meaning they occurred on top of those of NRTs.*”)

Second, the public health standard set forth in Section 911 of the Tobacco Act encompasses concerns about the effects of the availability of MRTPs on the use of smoking cessation products, including OTC NRTs. As discussed above, under Section 911, sponsors of MRTPs must address the effects of their products on smoking cessation (as well as smoking initiation) activities. One component of this question is whether the availability of MRTPs will reduce in whole or in part smokers’ use of FDA-approved, safe and effective smoking cessation products, including NRTs, to treat their nicotine dependence. *See* IOM Report at 184 (noting that “the net public health impact of the MRTP may be compromised to the extent that it reduced use of NRTs that ultimately led to smoking cessation.”) If smokers who are doing nothing to address their nicotine dependence are less likely to turn to FDA-approved smoking cessation products as a result of the availability of MRTPs, the public health suffers. Similarly, if current smoking cessation product users are more likely to switch to MRTPs than to continue their use of the FDA-approved therapy, or to use the two types of products simultaneously, thereby potentially diminishing the effect of the NRT, the public health suffers.⁵¹ These factors must be taken into account by FDA in reviewing MRTPs under Section 911 Manufacturers seeking an order under

⁵⁰ Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011 at 167.

⁵¹ FDA has indicated that a person using an approved NRT should *not* use any other product containing nicotine while using the NRT. *See* FDA 101 at 2. This suggests that the simultaneous use of an NRT and an MRTP will reduce the effectiveness of the former. It is up to the sponsor of the MRTP to prove otherwise.

Section 911 should be required to submit evidence concerning the effect of the marketing of MRTPs on the choice of smokers to use or not use NRTs.

Third, the parallels between smoking cessation drugs/devices and MRTPs are especially important when the smoking cessation product at issue, such as many NRTs, are available OTC. Both OTC NRTs and MRTPs are available directly to consumers without physician or pharmacy intervention, with the attendant risks of patient confusion and misuse. The studies used to support the switch from prescription to OTC build upon the initial FDA approval and evidence of safe use in an unsupervised setting that is sufficient to support a switch.⁵² The extensive review to which OTC NRTs are subjected – both during the initial review stage and then to support an Rx to OTC switch – is a good guideline for what is appropriate for MRTPs *before* a Section 911 order can issue. *See* IOM Report at 202 (noting that “[t]he studies required by FDA for products applying to switch from a prescription to over-the-counter (OTC) product may be useful in setting standards for studies in risk perceptions and risk communication Although label comprehension studies may not fully predict consumer behavior once a prescription drug reaches the market as an OTC product, they can assist in creating a label that communicates effectively. The committee believes that the standards for the label comprehension studies required for a prescription-to-OTC switch can be useful in the regulations of MRTPs.”).

The relationships between the structure that has been established for regulation of tobacco products—including section 911—and the regulation of NRTs require the development of a structure that coordinates FDA’s regulatory responsibilities in a way most conducive to protection of the public health. Regulation of both MRTPs and NRTs should proceed in coordination and should be designed to work toward a common goal. Section 918 of the FSPTCA directs the Secretary to take steps to review and consider approving and extending the use of NRT products for the treatment of tobacco dependence and to consider the use of such products for additional indications. In addition, it directs the Secretary to consider designation of such products for fast track research and approval. More than 18 months ago, a coalition of public health advocates filed a citizens’ petition requesting FDA to consider changes in the regulatory regime applicable to NRTs. As FDA considers adoption of procedures for the submission and consideration of evidence regarding MRTPs, the relationship between MRTPs and NRTs should be at an important focus of its attention.

V. Criteria for Recommended Studies and Analyses

The guidance states that “given the breadth of evidence needed to support the issuance of an order under section 911 . . . it is unlikely that a single study . . . or set of studies of one type will provide sufficient evidence to support issuance of an order.” This much is clear from the

⁵² For example, two non-nicotine smoking cessation devices, Chantix (varenicline tartrate) and Zyban (bupropion hydrochloride), are not available OTC, with FDA having identified significant adverse health effects associated with their use. *See, e.g.*, FDA Drug Safety Communication, “Chantix (varenicline) May Increase the Risk of Certain Cardiovascular Adverse Events in Patients with Cardiovascular Disease” (June 2011), available at www.fda.gov/Drugs/DrugSafety/ucm259161.htm ; FDA News Release, Chantix and Zyban Get Boxed Warnings” (July 2009), available at www.fda.gov/ForConsumers/ConsumerUpdates/ucm170356.htm.

statutory requirements. The guidance properly provides additional recommendations on the studies that are required.

The Institute of Medicine report deals in great detail with the nature of the studies that should be submitted. We believe that the guidance would be improved by incorporation of much of the material in the Institute of Medicine report. Although little in the guidance is inconsistent with that report, the level of detail provided in the report would prevent abuse, increase the consistency of the information presented, and would be helpful to the agency in formulating a procedure for review of applications.

The guidance appropriately suggests that actual use studies “should allow consumers to interact freely with the product in real-world conditions.” (p. 25, l. 983-84) In addition, the extensive list of issues to be assessed (l. 986-1000) is helpful and instructive.

A. Human Abuse Liability

The list of criteria for studies of human abuse liability properly includes assessment of factors that influence the speed and efficiency of nicotine delivery and the formation of unprotonated nicotine, including the presence of pharmacologically active constituents and ingredients and design features.

B. Consumer Perception and Understanding

Accurate evaluation of consumer perception is essential for the evaluation of the effect of modified risk claims on the health of the population as a whole, as well as an evaluation of the effect of such claims on specific demographic groups. Since overall population effect depends on which products the consumer chooses and since consumer product choice is greatly affected by claims regarding the health effects of tobacco products, consumer perception studies are critical in FDA’s evaluation of applications under Section 911.

The guidance properly advises applicants to consider several variations of the proposed claims on labels and advertisements. Submission of data regarding such variations provides important insights both to the agency in evaluating the application and to the applicant in designing marketing materials and studies to measure their effect.

C. Secondary Data Analysis and Computational Modeling

The guidance recognizes that computation modeling may be an important element in an MRTP application. Given the numerous factors that affect consumer behavior and the complexity of developing a model that can accurately predict consumer behavior, it will be critical that modeling play role, but also that FDA ensure that each model to held up to rigorous scrutiny and be the subject of public and well as expert review. Once again, we recommend the thoughtful analysis of the Institute of Medicine and incorporation in the guidelines of its recommendations.

D. General Principles for Scientific Studies and Analyses

The guidance contains a substantial list of general principles to govern scientific studies and analyses. (p. 28, l. 1092-1112) All the principles stated are valid and appropriate and consistent with good scientific standards. Among the principles is “oversampling of populations that are particularly likely to be affected, positively or negatively, by the marketing of the product.” We believe that this principle should be given greater emphasis and visibility in light

of its importance. Moreover, recognition of this principle underscores the necessity for FDA to have access to all marketing and product development studies conducted by or for the applicant. Without having such studies, it will not be possible to identify all the populations likely to be affected by the marketing of the product. For example, marketing studies might reveal that a given product was being developed to appeal to recent immigrants from a certain area of the world. In such a case, oversampling of those in this demographic group would be important. Without having the relevant marketing studies, there might be no way to identify the target demographic group.

VI. Institute of Medicine Recommendations Regarding Independent Testing and Governance

Although the guidance contains valid recommendations designed to ensure the quality and integrity of data from studies and analyses, it does not incorporate several recommendations made by the Institute of Medicine regarding the need for independent governance of such studies and testing. We believe that adoption of these Institute of Medicine recommendations would greatly strengthen the guidance and that, in their absence, the quality of the data presented to FDA in MRTP applications may suffer, to the detriment of sound decision-making. The guidance makes an apparent presumption that applicants will submit applications that make full disclosure of relevant information and are made in good faith. Unfortunately, experience indicates that such presumptions are not valid for the major tobacco companies. Accordingly, the recommendations made by the Institute of Medicine that are designed to improve the integrity of the scientific data presented to the FDA in connection with modified risk applications are of great importance and should be implemented.

The Institute of Medicine made two important recommendations regarding the governance of studies.⁵³

1. MRTP should consider the use of independent FDA- approved third parties to undertake one or more key functions, including the design and conduct of research, the oversight of specific studies and the distribution of sponsor funds.

This recommendation was based on the conclusion stated by the Institute of Medicine panel, that “it has been established in public records and as a matter of law that the tobacco industry has engaged in illegal and improper practices, including the destruction and manipulation of scientific data” and that as a result the industry is “profoundly isolated from the mainstream scientific community.” . As a result of the tobacco industry’s past abuse of science and the scientific method, many of the most prominent research universities have adopted policies prohibiting tobacco industry funding of research. As a practical matter, this means that the many qualified investigators will not work directly for the industry and that studies submitted by industry researchers would lack comparable credibility.

The IOM report correctly characterizes the historical record. There is a massive record demonstrating perversion of the scientific process by the tobacco industry over the course of many decades. This record includes evidence of suppression of research results, deliberate withholding of relevant records, and participation in a massive conspiracy to prevent the public

⁵³ Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011 at 243-44.

from learning the truth about the health effects of tobacco products—the very subjects of the relevant research regarding MRTPs.⁵⁴ Industry arguments that this history should be ignored lack credibility. Moreover, even if it were true that the industry could be trusted to conduct scientific research under appropriate standards, the credibility of the results of such research would still be widely questioned.

The result of this history is that, absent adoption of a new paradigm for the governance of research, regulatory research concerning these applications will be both less credible and, likely, of a lower quality than it should be.

The guidance and subsequent regulation issued by FDA should take account of these facts and address the recommendations made in the IOM Report to put procedures in place to ensure the independence and quality of the evidence being submitted to FDA.

2. FDA should require all MRTP sponsors to place all data generated in the development and marketing of the MRTP in a public repository selected by FDA.

Implementation of this recommendation would both add credibility to the research on which MRTP applications are based and add considerably to the science base available for future research. Appropriate exceptions could be made for data that is legitimately a trade secret or commercially confidential.

3. FDA should require that studies submitted in support of a MRTPA adhere to established standards and principles of good research governance, including appropriately qualified investigators, transparency, independent institutional review board or ethical review, and adherence to the Common Rule.

This standard is of course appropriate. FDA should ensure that the specific provisions of the guidance are sufficient to ensure that this standard is met.

VII. Post-market Surveillance and Studies

The guidance implements section 911(i), which requires post-market surveillance and studies in connection with an order permitting the marketing of MRTPs. As indicated in the guidance

Post-market surveillance involves the identification and collection of unanticipated and undesired events related to the tobacco product once it is introduced to the market; post-market studies generally are prospective, have well-defined study objectives and require active recruitment compared to surveillance. (p. 29, 1143-46)

Because so many of the essential studies required for issuance of such an order require predictions about consumer perception and consumer behavior, it is essential to require post-market surveillance and studies to determine whether such predictions were accurate and whether the actual effect of the marketing of the product for which an order was issued is having its expected effect. Moreover, as indicated in the guidance, actual marketing of a product will

⁵⁴ U.S. v. Philip Morris, supra, note 3.

involve the exposure of a much larger population to the product than in premarket studies and the product will be available for longer periods. Under such circumstances, it would not be surprising if actual experience diverged from predictions. To the extent that such divergence occurs, it is important for FDA to know about it promptly. Thus, the requirement for annual reporting of post-market surveillance and studies is appropriate and necessary.

FDA has substantial experience implementing post-market surveillance and studies for drugs and it can draw on this experience in establishing criteria for the evaluation of protocols for such surveillance and studies. The scope of post-market surveillance covers both passive surveillance and active surveillance. The guidance should be amended to provide for independent assessment by third parties with no connection to the tobacco product manufacturer.

In addition, FDA should establish provisions calling for automatic revocation of modified risk orders in the event that manufacturers fail to conduct adequate post-market surveillance or post-market studies. Once a modified risk order has been issued and modified risk claims are made for a product, FDA needs this authority in order to ensure that post-market activity actually proceeds as required by the guidance and by the order.

In the event that FDA issues an order permitting modified risk claims, it is essential that the order be expressly conditioned on the manufacturer's undertaking to ensure that specifically designated post-market studies and surveillance be done. The order should expressly state that in the event such post studies and surveillance are not done and submitted to FDA in accordance with the terms of the order, the order will be nullified and appropriate enforcement action taken against the non-compliant manufacturer.

Sincerely,

Campaign for Tobacco Free Kids
American Cancer Society – Cancer Action Network
American Heart Association
American Lung Association
American Association for Cancer Research
Legacy
Tobacco Control Legal Consortium