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March 22, 2011

Lawrence R. Deyton, M.D., M.S.P.H.
Director, Center for Tobacco Products
U.S. Food and Drug Administration
9200 Corporate Boulevard, Room 100
Rockville, MD 20850

Re: Philip Morris USA Inc. Report on the Use of Menthol in Cigarettes

Dear Dr. Deyton:

Altria Client Services (ALCS), on behalf of Philip Morris USA Inc. (PM USA),¹ provides the attached written report summarizing the science and evidence on the impact of the use of menthol in cigarettes on the public health. The Family Smoking Prevention and Tobacco Control Act tasked the Tobacco Products Science Advisory Committee ("TPSAC") with producing for FDA a report and recommendations on this same topic (the "TPSAC Report").

When FDA determined that industry representatives would not be permitted to participate in drafting the TPSAC Report, it invited the industry to provide a separate report. We are providing this report to contribute our perspective to FDA as it considers the use of menthol in cigarettes.

The information in the attached submission is entirely available for public release.

If you have any questions, please contact me at (804) 335-2679.

Sincerely,

A handwritten signature in blue ink, appearing to read "James E. Dillard III", with a stylized flourish at the end.

James E. Dillard III

cc: via e-mail to TPSAC@FDA.HHS.gov

¹ Altria Client Services (ALCS) provides this information on behalf of PM USA. ALCS provides certain services, including regulatory affairs, to the Altria family of companies.

PM USA Report to the FDA on the Use of Menthol Cigarettes

Prepared and submitted by Altria Client Services on behalf of
Philip Morris USA
for the
Food and Drug Administration

March 22, 2011

This Information is Fully Releasable.

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Executive Summary

The Family Smoking Prevention and Tobacco Control Act (FSPTCA or the Act) tasks the Tobacco Products Scientific Advisory Committee (TPSAC) with producing for FDA a report and recommendations on the impact of the use of menthol in cigarettes on the public health, including among children, African Americans, Hispanics and other racial and ethnic minorities (the TPSAC Report).

The tobacco industry comprises many separate companies, each with its own perspective. When FDA determined that the industry representatives would not be permitted to participate in drafting the TPSAC Report, it invited the industry to provide a separate report. Philip Morris USA (PM USA)¹ welcomes the opportunity to provide this report to FDA summarizing the evidence on that question and our conclusions.²

Our review of the science- and evidence-based information demonstrates that regulatory actions or restrictions related to the use of menthol in cigarettes are neither necessary nor justified. Significant restrictions, like eliminating menthol in cigarettes, would not reduce the population harm caused by cigarette smoking, and would lead to severe and lasting unintended consequences detrimental to public health objectives and society.

Below we address the following topics:

1. Guiding Principles for FDA Decision-Making about Menthol Cigarettes
2. Assessment of Individual and Population Harm
3. Marketing
4. Assessment of Countervailing Effects
5. Impact of Menthol Related Regulatory Actions on Public Health and Society
6. Considerations for FDA

We provide key conclusions on each topic in this Executive Summary and further analysis and supporting information in the individual chapters. We also provide a detailed reference list and study summary tables as appendices. These detailed references and study summary tables support our analysis and conclusions, while promoting brevity and conciseness of this Report.

Chapter 1. Guiding Principles for FDA Decision-Making about Menthol Cigarettes

The Act requires FDA to take multiple, equally important considerations into account in assessing potential menthol-related regulatory actions or restrictions. These include scientific evidence concerning the risks and benefits to the population as a whole and information concerning countervailing effects, such as the creation of a significant demand for contraband tobacco products. The Agency must also adhere to Executive Orders that govern federal regulatory policy and procedure.

¹ Altria Client Services (ALCS) is making this submission on behalf of PM USA. ALCS provides certain services, including regulatory affairs, to the Altria family of companies. “We” is used throughout to refer to PM USA.

² We use the terms “use of menthol in cigarettes” and “menthol cigarettes” interchangeably in this Report. Both terms refer to cigarettes that are marketed by reference to their menthol characteristics or flavoring and which consumers recognize as containing menthol flavoring. The terms “cigarettes that do not use menthol” and “non-menthol cigarettes” are also used interchangeably, referring to cigarettes that are not so marketed or recognized.

FDA's assessment of menthol should first be guided by the six foundational principles we outlined in a December 22, 2009 submission:³

- Decisions should be science- and evidence-based.
- Clarity and transparency will promote compliance.
- Reasonable regulation requires a balanced approach.
- Adult consumers are entitled to accurate and non-misleading information about tobacco products.
- Regulated industry is an important resource for FDA as it implements the FSPTCA.
- Implementation should leverage other available federal government resources.

We also urge FDA to consider three additional points. First, adult tobacco consumer choice is an appropriate consideration for FDA in order to faithfully implement the Act in the manner that Congress intended. Second, decisions about menthol must reflect the present day legal and regulatory environment related to cigarettes. Third, FDA has a powerful array of tools to reduce the harm caused by menthol and non-menthol cigarette smoking without adopting unsupported menthol-specific regulatory actions.

Chapter 2. Assessment of Individual and Population Harm

The question at hand is *not* whether cigarettes, menthol or non-menthol, cause disease or other adverse health effects. They do. PM USA agrees with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases and is addictive. Smokers are far more likely to develop serious diseases, like lung cancer, than non-smokers. There is no safe cigarette. It can be very difficult to quit smoking, but this should not deter smokers who want to quit from trying to do so. To reduce the health effects of cigarette smoking, the best thing to do is to quit. This applies equally to menthol and non-menthol cigarettes.

Rather, the issue here is whether menthol cigarettes are *different* from non-menthol cigarettes in the context of harm. Unfortunately, the TPSAC appears to assess menthol cigarettes against a completely hypothetical, "counterfactual" environment where menthol cigarettes never existed. The more appropriate question to answer is whether menthol cigarettes are more harmful than non-menthol cigarettes.

In this PM USA Report, we rely on an established scientific and evidentiary framework to answer it. This framework defines population harm as a combination of measurable outcomes – primarily, health risks and smoking prevalence. To analyze the evidence concerning these and related outcomes, we applied a traditional science-based approach. This included identifying and examining the available evidence, giving the most weight to the most directly relevant information and classifying the strength of the scientific evidence.

With respect to evaluating the strength of the scientific evidence, we urge FDA to follow the well-established and widely accepted classification system described in the 2004 Surgeon

³ See Letter from James E. Dillard, Senior Vice President, ALCS Regulatory Affairs, to docket FDA-2009-N-0294, December 22, 2009 (Guiding Principles for Implementation).

General’s Report⁴. This approach is informed by a long history of use in the context of tobacco products, relies on terms that are consistent with common and scientific usage, and takes a risk assessment approach.

The classification system that TPSAC proposes, based on the concept of “equipoise,” is not an appropriate tool for evaluating the menthol question at hand. This system arose in a unique historical context – establishing veterans’ eligibility to receive service-related benefits – that does not apply here. Also, this approach is entirely untested in the context of tobacco products. Further, it introduces confusion and bias and is too imprecise to support informed and transparent decision-making. Finally, it does not comport with scientific integrity principles issued by the Obama administration.⁵

To address the ultimate question about population harm, we applied the 2004 Surgeon General’s criteria to answer the following questions.⁶

APPLYING THE 2004 SURGEON GENERAL’S CRITERIA TO THE CRITICAL QUESTIONS	
Critical Question	Conclusion
Does menthol alter the inherent toxicity of cigarette smoke?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in the inherent toxicity of smoke.
Do menthol cigarettes affect average daily smoke exposure differently than non-menthol cigarettes?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in average daily smoke exposure.
Is there a difference, caused by menthol, in the health risks of smoking menthol and non-menthol cigarettes?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and increased health risk.
Do menthol cigarettes affect smoking initiation differently than non-menthol cigarettes?	The evidence is inadequate to infer the presence or absence of a causal relationship between the use of menthol in cigarettes and smoking initiation.
Do menthol cigarettes affect dependence differently than non-menthol cigarettes?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and increased dependence.
Do menthol cigarettes affect smoking cessation differently than non-menthol cigarettes?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and smoking cessation.

⁴ USDHSS (2004).

⁵ Memorandum for the Heads of Executive Departments and Agencies, from John P. Holden, Assistant to the President for Science and Technology and Director of the Office of Science and Technology Policy, issued December 17, 2010, at 1.

⁶ These conclusions are consistent with and further substantiated in our March 2010 and June 2010 Submissions.

APPLYING THE 2004 SURGEON GENERAL'S CRITERIA TO THE CRITICAL QUESTIONS (CONT.)	
Critical Question	Conclusion
Do menthol cigarettes affect smoking prevalence differently than non-menthol cigarettes?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and smoking prevalence.
Do menthol cigarettes affect population harm differently than non-menthol cigarettes?	No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in population harm.

Taken as a whole, the scientific evidence demonstrates that there is no unique menthol effect on the components of population harm. Thus, menthol cigarettes do not affect population harm differently than non-menthol cigarettes. Menthol cigarettes are no more harmful than non-menthol cigarettes.

Chapter 3. Marketing

PM USA is committed to responsibly marketing its cigarette brands by building relationships between those brands and adult smokers while using methods designed to minimize reach to unintended audiences. Our responsible marketing practices reflect a fundamental approach that kids should not smoke or use any tobacco products. PM USA does not direct any of its cigarette brand marketing to persons who are under legal age or to non-smokers. And PM USA markets its menthol cigarette brands using the same marketing approaches as for its non-menthol brands.

In the declining U.S. cigarette market, brand competition is intense. PM USA maintains or grows its cigarette brand market share by encouraging adult smokers of PM USA cigarette brands not to switch to, or make alternate purchases of, competitive cigarette brands; and by encouraging competitive brand adult smokers to make alternate purchases of, and to switch to, PM USA cigarette brands.

The TPSAC Report relied, in part, on selected historical industry documents to speculate on a number of factors claimed to influence consumer choice of menthol cigarette brands, including “targeting” of marketing communications; the use of color and imagery in marketing and advertising; and perception of risk. We demonstrate in Chapter 3 why TPSAC’s conclusions in these areas are incorrect and unsubstantiated by the evidence.

Chapter 4. Assessment of Countervailing Effects

The Act requires FDA to take into account the countervailing effects of potential menthol-related regulatory actions or restrictions. Congress intended FDA to take concerns about countervailing effects as seriously as concerns about the other risks and benefits to the population as a whole, its effects on initiation, and its effects on cessation.

PM USA provided a lengthy, detailed and well-sourced written report to TPSAC and FDA⁷ summarizing the potential countervailing effects of a ban on menthol cigarettes. That report demonstrates that radical regulatory action, such as eliminating menthol in cigarettes from the market, would be certain to trigger a series of lasting and severe unintended consequences and other countervailing effects detrimental to public health and to society.

A recent U.S. Government Accountability Office report also underscored that numerous incentives for and manifestations of contraband activity already exist within the current tobacco regulatory environment.⁸ Additionally, many other stakeholders similarly provided information to TPSAC demonstrating the existence of global contraband and counterfeit market that has the capacity to supply the U.S. market with illicit menthol cigarettes should the opportunity be created for them.

The TPSAC Report acknowledges the potential for contraband cigarettes existing, should FDA ban or restrict menthol cigarettes.⁹

FDA should not propose any actions to eliminate or otherwise restrict menthol cigarettes -- a product that millions of adult consumers use today -- without first (i) consulting with law enforcement and other relevant government authorities on the extent of the existing and potential expansion of a contraband market, and (ii) obtaining their assurances that they have the resources to respond to a substantial increase in contraband. FDA should conduct this consultation openly, publicly and transparently with all relevant stakeholders, including other government agencies.

Chapter 5. Impact of Menthol Related Regulatory Actions on Public Health and Society

The assessments of individual and population harm (Chapter 2) and countervailing effects (Chapter 4), independently and together, provide compelling evidence that regulatory actions or restrictions related to the use of menthol in cigarettes are not warranted by the science and are not necessary. It bears special mention that the U.S. government similarly has said, in official papers filed with the World Trade Organization, that banning menthol cigarettes is not appropriate to protect public health.

Chapter 6. Considerations for FDA

The science and evidence demonstrate that regulatory actions or restrictions related to the use of menthol in cigarettes are not warranted. That said, we are aware of the ongoing debate respecting issues of menthol cigarettes and offer some additional perspective to contribute constructively to the Agency's consideration of these issues. For example, the Agency could consider additional research on topics, such as menthol-specific interactions on smoking initiation, where the evidence could be more robust. Additionally, the Agency could consider

⁷ *Countervailing effects of a ban on menthol cigarettes*, prepared and submitted by ALCS on behalf of PM USA, December 30, 2010.

⁸ GAO (2011).

⁹ See TPSAC Report, *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*, Chapter 8, available online at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pdf>

possible actions to further ensure that adult smokers are fully informed respecting menthol in cigarettes. And FDA could consider whether public education campaigns and programs would be appropriate ways to address concerns about any consumer perceptions that are supported by the science. We address each of these considerations in the final chapter of this Report.

The Act has been in place for less than two years and FDA is in the midst of implementing its substantial provisions that are bringing sweeping changes for the tobacco industry and adult tobacco consumers. These provisions provide ample opportunity for FDA to undertake an overall approach to reducing the harm from cigarette smoking. Sound public policy warrants that FDA give these provisions an opportunity to achieve their intended purposes before proposing further or supplemental – and possibly countervailing – steps.

Chapter 1. Guiding Principles for FDA Decision-Making about Menthol Cigarettes

The FSPTCA authorizes FDA to adopt tobacco product standards if FDA “finds that a tobacco product standard is appropriate for the protection of the public health.”¹ In making such a finding, FDA must take multiple considerations into account.

One is scientific evidence concerning: (i) the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard; (ii) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (iii) the increased or decreased likelihood that those who do not use tobacco products will start using such products.²

Other equally important considerations are the “technical achievability of compliance with a proposed standard” and “all other information submitted in connection with a proposed standard, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or nontobacco users, such as the creation of a significant demand for contraband or other tobacco products that do not meet the requirements of this chapter.”³ Further, the Agency must adhere to Executive Orders that govern federal regulatory policy and procedure.⁴

FDA has stated that it will consider the TPSAC Report, as well as other scientific evidence concerning menthol cigarettes, and determine what actions, if any, are warranted.⁵ In so doing, the Agency has an important opportunity to demonstrate that it will base decisions about tobacco products on scientific evidence.

We hope that FDA has been informed by our several substantive submissions and presentations,⁶ in addition to our December 22, 2009 Submission which outlined six foundational principles important to the successful implementing of the FSPTCA:

- Decisions should be science- and evidence-based.
- Clarity and transparency will promote compliance.
- Reasonable regulation requires a balanced approach.
- Adult consumers are entitled to accurate and non-misleading information about tobacco products.

¹ FPSTCA § 907(a)(3)(A).

² *Id.* § 907(a)(3)(B)(i).

³ *Id.* § 907(b)(1-2).

⁴ *See, e.g.*, Exec. Order No. 12,866, 58 Fed. Reg. 51,735 (October 4, 1993); Exec. Order No. 13,563, 76 Fed. Reg. 3,821 (January 18, 2011).

⁵ *See* “FDA Remarks on the Report and Recommendation on the Public Health Impact of Menthol Cigarettes,” <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm247617.htm?>

⁶ *See* PM USA submissions to FDA dated March 22, 2010; PM USA submission to FDA dated June 30, 2010; PM USA presentations to TPSAC dated July 15, 2010; and PM USA submission to FDA dated December 30, 2010. We incorporate these submissions, which are part of the TPSAC record on menthol, here by reference.

Guiding Principles for FDA Decision-Making about Menthol Cigarettes

- Regulated industry is an important resource for FDA as it implements the FSPTCA.
- Implementation should leverage other available federal government resources.⁷

We also urge FDA to consider the following three points.

First, Congress intended for FDA to respect adult tobacco consumer choice. To be sure, concerns about underage tobacco use and the public health impact of cigarettes motivated Congress to grant FDA authority to regulate tobacco products. However, Congress explicitly preserved tobacco products as products that adults may use. Congress stated that a purpose of the FSPTCA is “to continue to permit the sale of tobacco products to adults in conjunction with measures to ensure that they are not sold or accessible to underage purchasers.”⁸ It also prohibited FDA from banning all cigarettes.⁹ Together, these provisions reflect the policy determination that adult tobacco consumer choice is to be respected.

One such choice millions of them make is to smoke menthol cigarettes. In fact, more than 26% of U.S. adult smokers choose menthol cigarettes. Moreover, menthol has been an accepted flavor segment in the cigarette category for decades. FDA must carefully assess menthol based on these facts, not on some hypothetical, “counterfactual” model where menthol never existed. Sound policy analysis and decision making requires no less.

In stating these facts, we do not minimize in any way the issue of underage smoking. While adults comprise the vast majority of smokers¹⁰, we agree that any underage use of cigarettes – either menthol or not -- is a legitimate concern. PM USA, like many others, has worked towards addressing this issue, and in fact, youth smoking rates have dropped significantly since peak levels in the late 1990’s. As compared to those peak levels, current rates of reported past 30-day cigarette use represent declines of 66% (8th graders), 55% (10th graders), and 47% (12th graders).¹¹

Our point is that menthol cigarettes are very different from cigarettes with characterizing flavors as defined and prohibited by the Act. The U.S. government shares this view, and stated so in submissions to the World Trade Organization regarding the Act’s prohibition of clove cigarettes. For example:

149. Additionally, while a small fraction of adults smoke clove cigarettes (and, therefore will not, on balance, be affected by the ban), *a large number of adults smoke menthol cigarettes, both in terms of percentage of the population and in absolute numbers, and many cite them as their daily, regular cigarette.*

⁷ See Letter from James E. Dillard, Senior Vice President, ALCS Regulatory Affairs, to docket FDA-2009-N-0294, December 22, 2009 (Guiding Principles for Implementation).

⁸ FSPTCA § 3(7).

⁹ *Id.* § 907(d)(3).

¹⁰ Based on ALCS analysis of 2009 National Survey on Drug Use and Health public use data, 96.3% of past 30-day smokers are age 18 or older. NSDUH data are available for download at: <http://www.icpsr.umich.edu/icpsrweb/SAMHDA/series/64/studies?sortBy=7>.

¹¹ See <http://monitoringthefuture.org/pubs/monographs/mtf-overview2010.pdf>

189....It is simply not the case, as Indonesia submits, that clove cigarettes are smoked primarily by adults, *as are tobacco and menthol cigarettes....*

242. In contrast, increasing the scope of the ban to include *either one or both* of the noncovered flavorings – tobacco and menthol – would not fulfill Congress’s legitimate objective as it would prohibit the sale of cigarettes whose consumption by addicted adults is *far from “negligible,”* accounting for the vast majority of cigarettes sold and consumed in the United States.¹²

Second, decisions about menthol cigarettes must reflect the present day legal and regulatory environment related to cigarettes. Cigarette sales, marketing, and use have become substantially restricted over the last 15 years, and even more so since FSPTCA’s enactment in 2009. According to FDA, steps it has already undertaken (such as implementing the final rule restricting access and marketing of cigarettes to youth and the statutory ban on cigarettes with certain characterizing flavors) or is taking (such as implementing new graphic warning labels for cigarettes) will be even more effective in preventing the initiation of cigarette smoking, particularly among youth, and encouraging smokers to quit.¹³ Such steps are part of a broad, coordinated strategy to reduce tobacco use. This is in contrast to some data TPSAC emphasized, like selectively chosen industry documents relating to consumers or marketing of decades ago, long before the current regulatory environment.

Third, Congress gave the Agency a powerful array of tools to reduce the harm caused by cigarette smoking. Any regulatory actions and restrictions depriving adult smokers of menthol cigarettes would be a highly intrusive way to reduce harm. Such regulatory actions would infringe on adult consumer choice, depriving millions of adult smokers of a product they prefer. Significant menthol-specific restrictions also would impose enormous burdens upon federal, state, and local governments, including those responsible for law enforcement and budgets. And, they would intrude – with no rational scientific basis – on the legitimate business of the regulated industry and cause harm to hundreds of thousands of others across the tobacco value chain. Such steps should never be taken lightly, and certainly should not be taken at all when the scientific evidence is non-existent or sparse, conflicting, or of inadequate quality.

¹² U.S. WTO (2010). (emphases added); see also U.S. WTO (2011).

¹³ See, e.g., Press conference re: “Protecting Kids from Tobacco” (March 18, 2010), <http://www.fda.gov/TobaccoProducts/ProtectingKidsfromTobacco/default.htm>; Transcript for FDA’s Media Briefing on Ban on Cigarettes with Certain Characterizing Flavors (September 22, 2009), <http://www.fda.gov/NewsEvents/Newsroom/MediaTranscripts/ucm121371.htm>; Webcast for FDA’s Graphic Health Warnings Announcement (November 10, 2010), <http://www.fda.gov/TobaccoProducts/NewsEvents/ucm232556.htm>.

Chapter 2. Assessment of Individual and Population Harm

Population harm, as we use that term here, refers to the adverse health outcomes in the U.S. population resulting from the use of cigarettes. Population harm is a component of public health impact, which we address in Chapter 5.

We organize our assessment of population harm into three sections. First, we outline an established framework and identify the critical questions to be answered. We then describe our approach for weighing and classifying the relevant evidence to answer those questions. Finally, we answer the critical questions relating to health risk, smoking prevalence, and population harm of menthol cigarettes as compared with non-menthol cigarettes.

As shown next, the evidence is suggestive of no causal relationship between the use of menthol in cigarettes and

- changes in the inherent toxicity of smoke;
- changes in average daily smoke exposure;
- changes in the health risks from smoking;
- dependence;
- cessation-related outcomes;
- smoking prevalence.

With respect to smoking initiation, the evidence is inadequate to infer the presence or absence of a causal relationship.

Because there is no unique menthol effect on individual outcomes, menthol cigarettes do not affect population harm differently than non-menthol cigarettes. This collective evidence is, therefore, suggestive of no causal relationship between the use of menthol in cigarettes and changes in population harm. Menthol cigarettes are no more harmful than non-menthol cigarettes.

I. Analytical Framework

To begin, we emphasize a point we have made repeatedly over the last year: the question is not whether cigarettes, menthol or non-menthol, cause disease or other adverse health effects. They do. PM USA agrees with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers and is addictive. Smokers are far more likely to develop serious diseases, like lung cancer, than non-smokers. There is no safe cigarette. It can be very difficult to quit smoking, but this should not deter smokers who want to quit from trying to do so. To reduce the health effects of cigarette smoking, the best thing to do is to quit. This applies equally to menthol and non-menthol cigarettes.¹

¹ When the U.S. Surgeon General, the International Agency for Research on Cancer, and other government and public health authorities concluded that smoking causes lung cancer, heart disease, and chronic obstructive pulmonary disease, among other diseases, they did not distinguish between menthol and non-menthol cigarettes. They relied on epidemiology and other scientific evidence related to cigarettes that used menthol and cigarettes that did not.

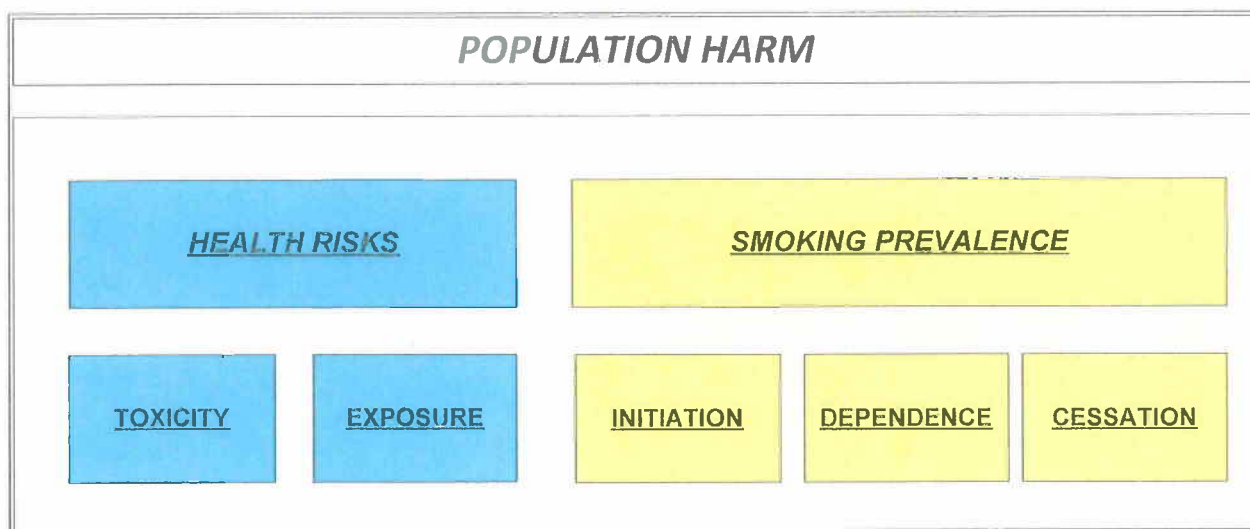
Rather, the issue is whether menthol cigarettes are *different* from non-menthol cigarettes in the context of harm. TPSAC's Report appears to assess menthol cigarettes against a completely hypothetical, "counterfactual" environment where menthol cigarettes never existed. The more appropriate question to answer is whether menthol cigarettes are more harmful than non-menthol cigarettes.

We address this question using an established framework for assessing population harm.

A. Population Harm Framework

Various models for assessing population harm from cigarette smoking have been proposed in the scientific literature. We use a framework derived from two recent models,² as depicted in Figure 2.1:

Figure 2.1. Measurable Outcomes for Population Harm Assessment



This framework defines population harm as a combination of measurable outcomes. The primary outcomes are *health risks* and *smoking prevalence*. Each primary outcome is informed by related secondary outcomes. Thus, health risks are determined by toxicity and exposure; smoking prevalence is determined by initiation, dependence, and cessation. Figure 2.2 summarizes methods to measure these outcomes.

² See IOM (2001) and Carter et al. (2009).

B. The Critical Questions

To assess the impact on population harm, we examine the following questions:

- **Is there a difference, caused by menthol, in the health risks of smoking menthol and non-menthol cigarettes?**
 - Does menthol alter the inherent toxicity of cigarette smoke?
 - Do menthol cigarettes affect average daily smoke exposure differently than non-menthol cigarettes?
- **Do menthol cigarettes affect smoking prevalence differently than non-menthol cigarettes?**
 - Do menthol cigarettes affect smoking initiation differently than non-menthol cigarettes?
 - Do menthol cigarettes affect dependence differently than non-menthol cigarettes?
 - Do menthol cigarettes affect smoking cessation differently than non-menthol cigarettes?
- **Do menthol cigarettes affect population harm differently than non-menthol cigarettes?**

II. Weighing and Classifying the Evidence

A. Weight of Evidence

We evaluated scientific studies, data, and other information using a weight of evidence approach. Thus, we gave greater weight to evidence most directly tied to population harm and less weight to evidence less directly linked to population harm. Figure 2.2 depicts this approach:

Figure 2.2. Weight of Evidence for Population Harm Assessment

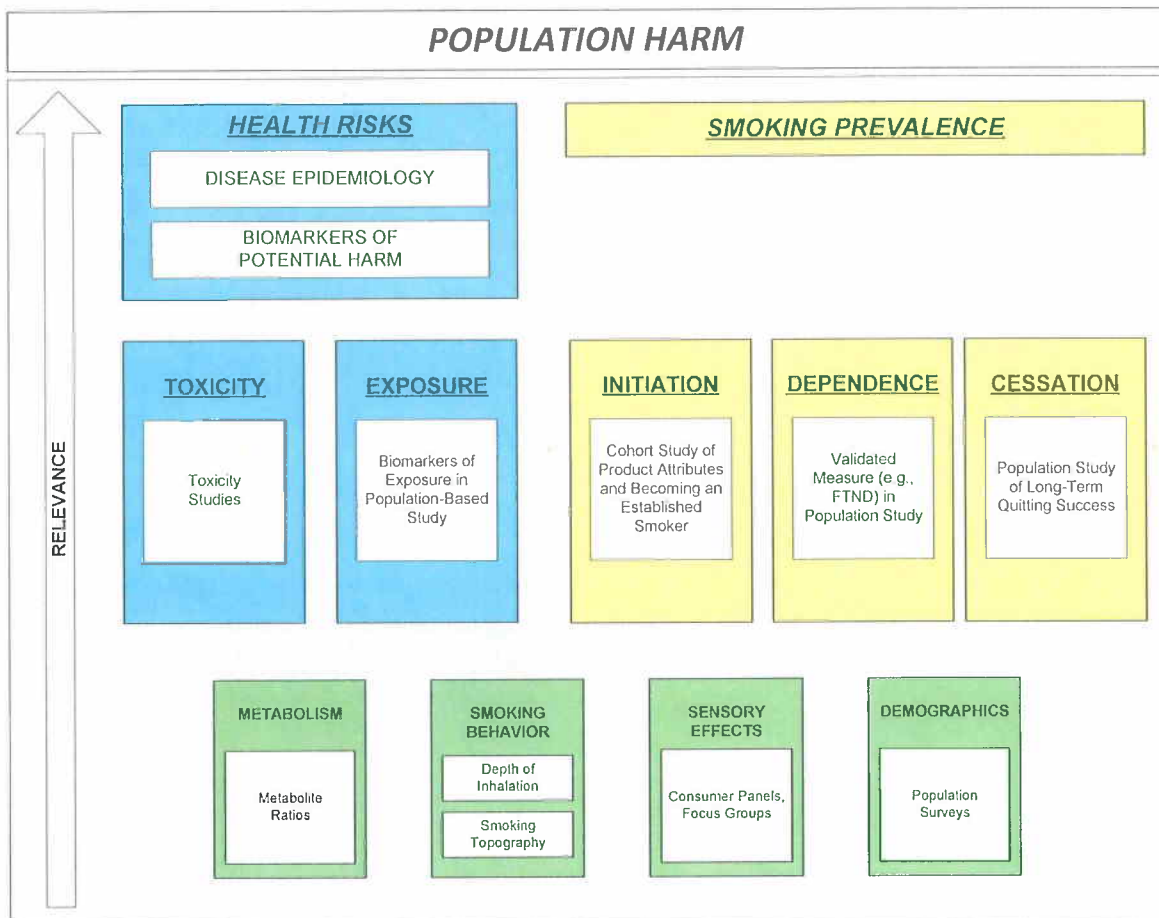


Figure 2.2 depicts primary outcomes, related secondary outcomes, and examples of direct and indirect methods for measuring each outcome (shown in the white boxes). The most relevant outcomes and measures are at the top; the least relevant are at the bottom.

Evidence from well-conducted, high-relevance studies have been given more weight than findings from less-relevant studies.

B. Classifying the Strength of Evidence

An appropriate evidence classification system supports sound regulatory decision-making by ensuring that proposed regulatory actions are supported by the scientific evidence pertaining to a potential risk.

1. Classification approach

A major aspect of classifying the strength of evidence has to do with causal inference. The 2004 U.S. Surgeon General Report described a four-tiered system to categorize the strength of scientific evidence:

- A. Evidence is **sufficient** to infer a causal relationship.
- B. Evidence is **suggestive but not sufficient** to infer a causal relationship.
- C. Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).
- D. Evidence is suggestive of no causal relationship.

These categories rely upon the Hill criteria³ to assess causal inference and provide a standardized way of classifying strength of evidence. We use this 2004 U.S. Surgeon General classification approach and urge FDA to do the same.

2. TPSAC's classification approach

Instead of following this well-established approach for evidence review and classification, the TPSAC inappropriately relied on a modified version of a relatively new, four-level approach outlined in a 2008 IOM Report for the Veterans Administration (IOM-VA Report).⁴ Moreover, the TPSAC significantly modified this untested approach and adopted the following four-level classification scheme based on the concept of “equipoise”:

- The evidence is sufficient to conclude that a relationship is more likely than not.
- The evidence is sufficient to conclude that a relationship is at least as likely as not (equipoise).
- The evidence is insufficient to conclude that a causal relationship is more likely than not.
- There is insufficient evidence to make a determination of strength of evidence.

There are several reasons TPSAC erred in using this approach. First, this approach arose in a unique context not relevant here – implementing a policy giving veterans the benefit of the doubt in claims for injury and illness resulting from military service. We are not aware of any other instance in which equipoise has been used to assess the strength of scientific evidence. The only other statutory application of the equipoise concept involved reparations to Japanese-Americans for their forced internment by the government during World War II.⁵ The policy drivers of such an approach – to provide veterans with benefits or to compensate victims – do not apply here.

Other policy rationales for the equipoise-based classification scheme are also inappropriate. For example, one rationale for establishing a presumption in favor of veterans was that they lacked the financial and other resources to prove scientific and technical elements of their claim.⁶ There is no such concern here. FDA has access to vast scientific and technical expertise throughout the federal government and within the scientific community. Another rationale was that veterans could not access information needed to prove their claims because it was designated as classified or secret.⁷ Again, there is no such concern here. FDA has statutory authority to obtain confidential and trade secret information from the regulated industry, and has done so.⁸

³ Hill (1965).

⁴ IOM (2008) at 19.

⁵ See 50 U.S.C. § 1989b-4(a)(3).

⁶ See IOM (2008) at 37, 42.

⁷ *Id.* at 326.

⁸ See, e.g., FSPTCA § 904(b).

Second, using the equipoise classification suggests policy-driven outcomes rather than objective, data-driven risk assessment based on scientific evidence. It is entirely untested in the context of tobacco products, in contrast to traditional approaches used by the U.S. Surgeon General, International Agency for Research on Cancer, and the National Toxicology Program

Third, the proposed equipoise classification is too imprecise to support informed decision-making. A designation of perfect equipoise – “as likely as not” – would signify that the evidence is evenly divided between supporting and not supporting the existence of a causal relationship. However, TPSAC proposes a much broader classification – “*at least* as likely as not.” This classification establishes a structural bias, because the *same* classification level would be used for evidence that is *at* equipoise and evidence that is *above* equipoise. At best, this is confusing. At worst, it can provide a vehicle for policy preferences to make weak evidence appear strong.

Finally, the proposed approach does not comport with scientific integrity principles issued by the Obama administration. By Executive Order, “each [federal] agency shall ensure the objectivity of any scientific and technological information and processes used to support the agency’s regulatory actions.”⁹ A December 17, 2010 memorandum provides guidance to federal agencies regarding scientific integrity, emphasizing that “[s]uccessful application of science in public policy depends on the integrity of the scientific process both to ensure the validity of the information itself and to engender public trust in Government.”¹⁰ The TPSAC’s proposed classification approach simply does not meet these standards.

III. Answering the Critical Questions

Our analysis draws on all the available evidence, particularly the detailed information provided in our March 2010 and June 2010 submissions, which are incorporated into this document by reference, and to which we refer FDA for more detail.¹¹ In addition, there now are available subsequent published literature and analyses. All this forms the basis for our analysis and conclusions. As noted above, we are also providing here a reference list of scientific evidence (Appendix A) and detailed study summary tables (Appendix B).

A. Background

1. The Sensory Experience

As described in our June 2010 Submission, we design our menthol cigarettes to meet the taste preferences of adult smokers who wish to smoke menthol cigarettes. We do this by balancing the amount of menthol with the design features that affect the amount of tar and menthol in smoke.

⁹ Exec. Order No. 13,563, 76 Fed. Reg. 3,821, at § 5 (January 18, 2011).

¹⁰ Memorandum for the Heads of Executive Departments and Agencies, from John P. Holden, Assistant to the President for Science and Technology and Director of the Office of Science and Technology Policy, issued December 17, 2010, at 1.

¹¹ *Submission re: March 30-31, 2010 Meeting of the Tobacco Products Scientific Advisory Committee*, prepared and submitted by ALCS on behalf of PM USA, March 22, 2010; *Background Information to Tobacco Products Scientific Advisory Committee, Menthol Discussion*, prepared and submitted by ALCS on behalf of PM USA, June 30, 2010.

Many studies have examined the effects of menthol *per se* on sensory responses. Research studies have shown that menthol *per se* produces a cooling sensation by binding with the TRPM8 channel and irritation by binding with the TRPA1 channel. Other reports in the scientific literature suggest that menthol *per se* can act as an anesthetic or analgesic, particularly for dermal application. However, mechanistic studies do not support a local anesthetic effect for menthol in the airways (respiratory tract, mouth and throat).

With regard to an analgesic effect, a desensitizing effect of menthol on nicotine-induced activation of TRPA1 channels has been observed in cultured cells. A published clinical study concluded that pre-treatment with menthol appears to desensitize the tongue to nicotine-induced irritation.¹² However, findings from a PM USA-funded clinical study indicate that menthol does not desensitize the upper respiratory tract to irritation caused by nicotine, even in the presence of a cooling sensation.¹³

In contrast to studies of menthol *per se*, there are very limited data on the sensory effects of menthol in cigarette smoke. The desensitizing effects of menthol observed in cell studies or in oral irritation models (tongue) should not be assumed to be the same as the effects of menthol in smoke or in the airways. Smoke contains a number of reactive molecules that can bind with TRPA1 receptors. The interaction of menthol with the TRPA1 channel, in the presence of numerous reactive smoke constituents, is likely to be more complex than the interaction of menthol alone. Published studies that have examined the interaction between reactive molecules and menthol at the TRPA1 channel have reported that such molecules eliminated menthol's ability to influence the activation of this channel.¹⁴

Unconjugated or free menthol has not been detected in the blood of individuals smoking menthol cigarettes.¹⁵ Thus, it seems unlikely that sensory effects resulting from the direct action of menthol from smoke occurs outside the airways. Whether menthol in cigarette smoke produces an anesthetic or analgesic effect on the respiratory tract has not been directly examined. Indirect evidence, however, suggests none. For example, studies of the effect of menthol cigarettes on depth of inhalation show no difference between menthol and non-menthol cigarettes.¹⁶ If menthol were exerting a significant physiological effect related to reducing sensations in the respiratory tract, these inhalation patterns would be expected to change.

In the framework for population harm, evidence about the sensory experience of smoking menthol cigarettes provides, at most, indirect information for answering the critical questions. Therefore, the current incomplete understanding of how menthol in smoke affects sensory responses and receptors does not impact the overall assessment of population harm. Yet, the TPSAC relied on sensory data regarding menthol *per se* to conclude biological plausibility for population harm.

¹² Dessierier et al. (2001).

¹³ Renner & Schreiber (Manuscript Submitted for Publication).

¹⁴ Karashima et al. (2007).

¹⁵ Ahijevych et al. (2002).

¹⁶ Jarvik et al. (1994); St. Charles et al. (2009); Ahijevych et al. (1996).

2. Demographics of Menthol Cigarette Use

The Tobacco Use Supplement to the Current Population Survey estimated that 26.6% of adult smokers in the United States smoke menthol cigarettes.¹⁷ The proportion of adult menthol smokers varies in different sociodemographic groups as menthol cigarette smokers are not a homogenous population. Several recent papers have examined the prevalence of menthol smoking and further characterized differences in gender, race, age, education, income and employment and other differences between menthol and non-menthol smokers.¹⁸

The comparison of menthol-related demographic patterns with patterns of health effects in certain U.S. subpopulations – African Americans in particular – have led to speculation that menthol may have a unique contribution to the health risks from smoking. Analyses of the general population and subpopulations, including African Americans, show that it does not. Several factors unrelated to menthol cigarettes, such as lack of control for confounding factors and social and environmental differences, are likely to explain observed disparities in health risks between different subpopulations.

B. Health Risks, Smoke Toxicity and Exposure

With respect to health risk, the effects of menthol in cigarettes have been extensively studied. Investigations provide direct evidence about the health risks (disease epidemiology), smoke exposure (biomarker studies) and the toxicity of smoke (non-clinical testing and the safe use of menthol in other products). A considerable amount of indirect evidence also exists (*e.g.*, study of puffing topography, effect on metabolism). We examine and summarize three main areas of concern as they relate to possible differences in health effects of menthol cigarettes compared with non-menthol cigarettes: (i) smoke toxicity, (ii) exposure and, (iii) health risks in humans.

1. Does menthol alter the inherent toxicity of cigarette smoke?

The safety profile of menthol has been extensively investigated in pre-clinical studies.¹⁹ Menthol has a long history of safe use in a wide range of consumer products. Further, the addition of menthol to cigarettes has been extensively studied using a variety of non-clinical tests including smoke chemistry, *in vitro* biological tests and animal studies.²⁰

During TPSAC's review of menthol, some members hypothesized that menthol might affect smoke toxicity by altering the metabolism of other compounds in smoke, particularly NNK and nicotine.²¹ However, the most definitive assessment of this possible effect has been investigated in the PM USA Total Exposure Study (TES), which found no significant effect of menthol on either NNK or nicotine metabolism based on evaluation of metabolite ratios. This information was presented at a public meeting of the American College of Clinical Pharmacology,²² and we have provided to FDA all data needed to replicate this analysis.

¹⁷ NCI (2010).

¹⁸ Rock et al. (2010); Cubbin et al. (2010); Lawrence et al. (2010).

¹⁹ Belsito et al. (2008); Bhatia et al. (2008).

²⁰ See Appendix Table B-3.

²¹ Benowitz et al. (2004).

²² Sarkar et al. (2010).

