

Center for Regulatory Effectiveness

1601 Connecticut Ave, NW – Suite 500

Washington, DC 20009

Tel: (202) 265-2383 Fax: (202) 939-6969

www.TheCRE.com secretary1@mbsdc.com

September 20, 2010

Sent via email and certified mail

Dr. Lawrence R. Deyton, MSPH, MD
Director, Center for Tobacco Products
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850
lawrence.deyton@fda.hhs.gov
ctpexecsec@fda.hhs.gov

Sent via email and certified mail

Office of the Ombudsman
Food and Drug Administration
5600 Fishers Lane
Room 14B03, HF-7
Rockville, MD 20857
informationquality@oc.fda.gov

Request for Correction, pursuant to the Information Quality Act and its Guidelines, of Information Being Disseminated by the Food and Drug Administration and its Center for Tobacco Products regarding Menthol Cigarettes and Public Health

Information for which Correction is Sought

At the March 30-31 meeting of the Tobacco Products Scientific Advisory Committee ("TPSAC"), representatives of FDA's newly-established Center for Tobacco Products ("CTP"), Drs. Joshua Rising and Allison C. Hoffman, employees of the CTP, made slide presentations, and accompanying verbal presentations, to the TPSAC. The focus of the meeting was consideration of the available scientific information on the impacts of smoking of menthol cigarettes on the health of individual smokers and the public.

The slide presentations and accompanying verbal presentations from March 30, 2010, that are the subject of this petition are --

1. "Menthol Cigarettes and Smoking Initiation," presented by Dr. Rising;
2. "Menthol Cigarettes and Nicotine Dependence," presented by Dr. Hoffman; and
3. "Menthol Cigarettes and Smoking Cessation," presented by Dr. Hoffman.

These slide presentations are being disseminated on the FDA/TPSAC website at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm180903.htm>. The FDA verbal presentations accompanying those slide presentations are recorded in a transcript at the same location on the FDA/TPSAC website.¹

¹ The full transcript of the meeting has an index that indicates the pages for the verbal presentations.

Center for Regulatory Effectiveness

In addition to the transcript, the FDA/TPSAC website contains a recording of the live webcast of the proceedings.

This petition does not seek correction of specific FDA statements being disseminated on the slides and in the transcript, because they are part of the record of the proceedings; rather, it seeks clear FDA acknowledgements, both to the TPSAC at its next meeting, and to the public in connection with the website materials, that the slide and verbal presentations, and the studies on which they are based, do not meet IQA standards, and were presented to the TPSAC for peer review purposes only.

Although this petition focuses on IQA defects in only several of the slide presentations, the accompanying verbal presentations, and the studies on which they were based, it is likely that the other slide presentations and verbal presentations and the underlying studies also contain IQA defects. Therefore it is recommended that the lack of IQA compliance be made in connection with all of the presentations rather than just those that are examined in detail in this petition.

Applicability of the IQA Standards

The applicable IQA standards for quality are contained in the IQA² and the IQA guidelines promulgated by OMB, HHS, and FDA.³ There can be no doubt that the subject presentations are disseminations of agency information within the meaning of the IQA and its guidelines, since they are being distributed on an FDA website as FDA information.

Although the presentations were made as part of a peer review proceeding within the meaning of the IQA peer review guidelines,⁴ they do not qualify as draft agency assessments submitted for peer review because they do not carry the disclaimer required by the peer review guidelines. The peer review guidelines require that agency assessments presented for peer review present or display the following disclaimer:

accompanying the slides.

² 44 U.S.C. § 3516, note.

³ The original OMB government-wide IQA guidelines setting out the basic quality standards for scientific information were published at 67 Fed. Reg. 8452 (Feb. 22, 2002). When we refer to the IQA guidelines herein, unless indicated otherwise we will be referring to those original OMB government-wide guidelines. The HHS guidelines, and the FDA guidelines contained within the HHS guidelines, conform to the OMB guidelines in most respects. The HHS and FDA guidelines can be accessed at <http://aspe.hhs.gov/infoquality/Guidelines/index.shtml>.

⁴ 70 Fed. Reg. 2664 (Jan. 14, 2005). The peer review guidelines are not limited to peer review of draft agency information; they also cover peer review of "third-party," or published, information/literature that has already been peer reviewed but is again being peer-reviewed as the potential basis for an agency determination. The peer review guidelines state that "if an agency plans to disseminate information supplied by a third party (*e.g.*, using this information as the basis for an agency's factual determination that a particular behavior causes a disease), the requirements of the [peer review] Bulletin apply, if the dissemination is 'influential.'" *Id.* at 2667.

Center for Regulatory Effectiveness

This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by [the agency]. It does not represent and should not be construed to represent any agency determination or policy.⁵

If agency information used in a peer review proceeding does not carry that disclaimer, the information is subject to the IQA standards.⁶ Instead of being presented as draft agency information presented for peer review purposes, however, the information in the slides and verbal comments were presented as unqualified FDA/CTP positions, and they were presented by employees of the agency and the slides all displayed the FDA logo and name.

Most of the FDA/CTP slides presented to the TPSAC cited specific published scientific studies as the basis for their statements, and the verbal presentations also explained that the slides were based on those studies. The published studies described and cited in the slides and in the accompanying verbal comments are considered "third-party" information under the IQA guidelines. If they had simply been presented to the TPSAC as references in a bibliography, they would not be subject to the guidelines; however, when FDA/CTP gave the appearance of relying on them (and if it does so in the future), they became subject to the IQA standards. The IQA guidelines are clear on this, stating:

[I]f an agency, as an institution, disseminates information prepared by an outside party in a manner that reasonably suggests that the agency agrees with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to these guidelines.⁷

In other words, an agency such as FDA/CTP cannot disseminate information that gives the appearance of relying on such third-party information (in this case, published studies), unless that third-party information meets IQA standards for quality. And even if the agency were to add the required disclaimer to the information it was providing to the TPSAC for review, that would still not relieve the agency of the responsibility for ensuring that any third-party studies it relies on in making a regulatory determination or other information dissemination meets IQA standards.

In the case of the agency slides and verbal presentations discussed herein, those slides and verbal presentations undoubtedly "reasonably suggest[]" that the agency agrees with the information [in the studies]," and therefore the third party studies described in the slides and the verbal presentations on them are subject to the IQA guidelines.

⁵ *Id.* at 2667, 2674.

⁶ *Id.* at 2667.

⁷ 67 Fed. Reg. at 8454. See also the Memorandum for President's Management Council from John D. Graham, Administrator of OIRA, dated June 10, 2002, at 6-7, available at http://www.whitehouse.gov/sites/default/files/omb/assets/omb/inforeg/iqg_comments.pdf.

Nature of the Non-Compliance with IQA Standards

The basic IQA standard at issue in this petition is the quality standard of "objectivity." Under the guidelines, "objectivity" requires that information be presented in an "accurate, clear, complete, and unbiased manner," with disclosure of "error sources affecting data quality"⁸ The agency must also ensure that the information is "accurate, reliable, and unbiased," and that the "original and supporting data shall be generated, and the analytic results shall be developed, using sound statistical and research methods."⁹ Agencies must ensure information quality under the IQA by "1) clearly identifying the limitations inherent in the information dissemination product (*e.g.*, possibility of errors, degree of reliability, and validity) so users are fully aware of the quality and integrity of the information ... 2) taking reasonable steps to remove the limitations inherent in the information, and 3) reconsidering delivery of the information"¹⁰

Several of the studies presented in the agency slides and verbal presentations, and the slides and verbal presentations, are examined below for compliance with these basic IQA quality standards. As will be seen, both the studies and the agency presentations suffer from significant IQA quality defects.¹¹

In the case of the studies, in general they have quality defects in the form of significant methodological limitations that make them unreliable, as well as inconsistencies that not only demonstrate their unreliability but also indicate bias. Those limitations, and problems with reliability of the studies, were not explained in the FDA presentations.

In the case of the slides and verbal presentations accompanying the slides for those studies, in general they suffer from being incomplete and biased because they do not disclose error sources, or limitations, of the studies, and do not present conflicting data and information contained in other studies that are referenced in the presented studies.

Examples of IQA Quality Defects in Specific Portions of the FDA/CTP Presentations

⁸ 67 Fed. Reg. at 8459.

⁹ *Id*

¹⁰ Memorandum M-05-04 for the Heads of Executive Departments and Agencies, dated Dec. 17, 2004, from OMB's Deputy Director for Management, setting out "Policies for Federal Agency Public Websites," including policies for ensuring information quality under the IQA and its guidelines, available at <http://www.whitehouse.gov/sites/default/files/omb/assets/omb/memoranda/fy2005/m05-04.pdf>.

¹¹ A scientific study that has been published as peer-reviewed literature is not exempt from the IQA standards. Prior peer review establishes a presumption of objectivity, but that presumption is rebuttable by a showing of non-compliance. 67 Fed. Reg. 8452, 8454, 8459 (Feb. 22, 2002); 70 Fed. Reg. 2664, 2671 (Jan. 14, 2005) ("[P]rior peer review and publication is not by itself sufficient grounds for determining that no further review is necessary.").

Center for Regulatory Effectiveness

Below we have analyzed eight of the studies that the FDA and its CTP presented to the TPSAC, as well as the agency slides and verbal presentations of those studies. The number of analyses reflects only the limits of CRE's resources, it does not indicate that the other smoking initiation/cessation studies and surveys used in the FDA's presentations are IQA-compliant.

Each of CRE's analyses has been posted on CRE's TPSAC Interactive Public Docket ("IPD") for public review and comments.¹² These posted documents are "living analyses" since CRE will be updating them based on comments received from stakeholders. The analyses contained in this petition supplements the analysis on the CRE website.

1. Hersey JC *et al.* 2006 Are menthol cigarettes a starter product for youth? *Nicotine & Tob Res* 8(3):403-13.

At the March 30-31 meeting of the TPSAC, three of the FDA slides and related verbal presentations included material that they cited as taken from this publication. Although the FDA presentations were directed to TPSAC members, the meeting was public, and the slides and a transcript of the verbal comments accompanying the slides are being disseminated on the TPSAC website. The meeting was also televised via webcast.

Dr. Joshua Rising of FDA, in his talk and slide presentation on "Menthol Cigarettes and Smoking Initiation" (indicated to be made on behalf of FDA), presented a slide based on this publication showing percentage of menthol cigarette use declining from 62 to 53 percent in middle school, for those smoking less than one year and those smoking more than one year, respectively, and to 46 and 42 percent in high school for the same classes of smokers. (Slide 8) In his comments on those statistics, Dr. Rising indicated that this might indicate "individuals transitioning from menthol cigarettes to nonmenthol cigarettes." (Tr. at 188-89). In the context of the presentation with its citation to the Hersey *et al.* article, the implication was that such statistics were an indication that menthol cigarettes were operating as a "starter product" for youths between the ages of 11-14 (middle school) and 14-18 (high school). The slide also referenced the National Youth Tobacco Survey ("NYTS") 2002 as a source of the data.

At the same TPSAC meeting, Dr. Allison Hoffman of FDA gave a slide presentation and accompanying comments, also indicated to be on behalf of FDA, on the subject of "Menthol Cigarettes and Smoking Cessation." She presented a slide (No. 15) based on Hersey *et al.* which stated that it found that "Adolescent menthol smokers were less likely to be 'seriously thinking about quitting'" and that "Adolescent menthol smokers were more likely to have sought help in quitting." (Emphasis from slide, not publication.) Dr. Hoffman's comments on this slide provided a biased perspective on what appears otherwise to be an inconsistency (seeking help appears to indicate a more serious intention to succeed at quitting). She told the TPSAC that the Hersey *et al.* study found that adolescent menthol smokers were significantly less likely to be seriously thinking about quitting, and that "the good news is that those [menthol smokers] who did try to quit were significantly more likely to have sought help in quitting." (Tr. at 216.) The clear implication of her comments seemed to be that young menthol smokers had less interest in quitting, and when and if they did try to quit, they needed (more) help in their attempt.

¹² <http://www.thecre.com/scur>.

Center for Regulatory Effectiveness

Dr. Hoffman also gave a presentation to the TPSAC on the same day on "Menthol Cigarettes and Nicotine Dependence." Slide 10 concerned the Hersey *et al.* study. It stated that in youth in grades 6 through 12, the study found that "[t]eens who regularly smoked menthol cigarettes had **45% greater odds of scoring higher** on the Nicotine Dependence Scale for Adolescents." (Original emphasis) The slide also noted that the study differentiated between weekdays and weekends.¹³ In her comments on the slide, Dr. Hoffman emphasized that the study discriminated between the first cigarette on a weekday and on a weekend. (Tr. at 201).

The Hersey *et al.* publication and the FDA presentations to the TPSAC using that publication present two somewhat different issues. First, is the Hersey *et al.* study and the data it presents sufficiently reliable and accurate as a basis for any TPSAC or FDA position on the above points? Second, did FDA accurately and objectively represent the study findings in their slides and verbal presentations? The IQA and its guidelines require that when an agency relies on outside information in one of its disseminations, that information must meet IQA standards, in this instance meaning that it must be "objective" and "accurate, reliable, and unbiased." And the agency (FDA) dissemination based on the outside information must also be "objective" and "accurate, reliable, and unbiased." The IQA guidelines require that for a study to be "accurate, reliable, and unbiased," "error sources affecting data quality should be identified and disclosed to users" and "analytic results shall be developed, using sound statistical and research methods."¹⁴

The initial issue, then, is whether the Hersey *et al.* study is sufficiently reliable to be the basis for an FDA dissemination. The second is whether those study results were accurately and objectively portrayed by the FDA presenters. As will be seen, the answer to both issues is No.

a. Reliability of the Hersey *et al.* study.

At the outset, it should be noted that the study's analysis and conclusions are dominated by speculation rather than concrete findings, with terms like "possibility," "may"/"might," and "suggest" occurring with great frequency.¹⁵

The study is based on just two years of the biennial National Youth Tobacco Survey

¹³ The FDA practice of sometimes adding bold and underlining emphasis to study findings that appear to support a position that menthol cigarettes are more dangerous than non-menthol cigarettes, while not adding emphasis to studies going the other way, is, by itself, a clear example of bias in dissemination under the IQA and its guidelines.

¹⁴ 67 Fed. Reg. 8452, 8459 3d col. (Feb. 22, 2002). The term "objective" comes from the statute, and the OMB Guidelines define "objectivity" to encompass accuracy, reliability, and absence of bias, as well as transparency with regard to error sources and the need for sound research and statistical methods in analysis. *Id.* As noted above, FDA's IQA guidelines require disclosure of the limitations of studies.

¹⁵ It is common to phrase the title of a study that is mainly exploratory as a question, whereas a study that contains some concrete findings that the authors (or the journal editors) believe are more supportable will have a title that is a positive statement. The title to the Hersey *et al.* article is in the form of a question rather than a positive statement, indicating that it is to be regarded as exploratory and speculative.

Center for Regulatory Effectiveness

("NYTS"), 2000 and 2002. (Datasets from the 2004 and 2006 surveys have been published. The 2006 survey results are the latest; there was no NYTS data collection in 2008.) The NYTS is based on a voluntary, self-administered questionnaire given to thousands of youths between the ages of 11 and 18. Roughly 36,000 youths responded to the 2000 and 2002 surveys. In other words, the survey population was comprised mainly of youths who were too young to legally purchase cigarettes, and who therefore must have obtained them some other way.¹⁶

Such means would most likely include obtaining them from persons who can purchase them legally, from friends who have obtained them from such persons or through other means, or by pilfering them from parents or older siblings. Youths under 18 are therefore, of necessity, opportunistic smokers, and are likely to obtain individual cigarettes without the packaging and without knowing the brand, or without paying much attention to it if they do observe it. As opportunistic smokers, they probably are not selective in what they smoke and probably smoke both menthol and non-menthol cigarettes according to what they can get (or are offered). And whether they even know, or care about, the difference between menthol and non-menthol cigarettes cannot be determined. The survey questionnaire used in the 2000 and 2002 NYTS asked only a single question about smoking of menthol cigarettes. That question is likely to have been confusing to young opportunistic smokers because it asked if "the brand of cigarettes you usually smoked during the past 30 days [is] mentholated?" If a youth considered himself/herself only a rare or irregular smoker, and did not pay attention to the brand of cigarette, and was not even sure of the difference between a menthol and non-menthol cigarette, could they have answered that question reliably? To put it another way, is it likely that a 12-year-old who had smoked one or two cigarettes borrowed from friends during the last 30 days could be counted on to give a reliable answer to such a question?¹⁷ The answer is obviously No. Consequently, the basic data source for the study (a self-administered youth survey with confusing questions) is inherently unreliable.

Turning from the data source for the Hersey *et al.* study to its analysis, the question again is whether it provides reliable information.

The most notable aspect of the study is its use of the loaded term "starter product." The study's title ("Are menthol cigarettes a starter product for youth?") and its conclusion ("the study indicates that menthol cigarettes may be a starter product") both use the term. And FDA's use of the study in a presentation on youth smoking initiation indicates some reliance on this basic thrust of the article.

But what exactly is a "starter product," or what do the authors mean by their use of the term? They don't define the term. A familiar use of the term comes from the business world, indicating a product that is part of a marketing strategy to induce customers to try a new type of product by offering a lower-priced, stripped-down or basic version to get a customer to try the

¹⁶ The legal age for purchasing cigarettes is 18 in all but three States, and 19 in those other three.

¹⁷ The data from this question might not only have been unreliable, it might well have been distorted in the direction of indicating more menthol cigarette use by younger smokers. It is a given that more women smoke menthol cigarettes, and if a youth pilfered an occasional cigarette from his mother or older sister because it was easier than pilfering from a father or older brother, the youth would probably smoke more menthol than non-menthol cigarettes.

Center for Regulatory Effectiveness

type of product or brand in hopes that they will then move up to a higher-priced, more features-laden model. A variation on this is the offering of a lower-priced product that subsequently requires the customer to spend more than they did on the original product. Easily recognizable example of this marketing strategy are low-priced razors that then require repeat purchases of expensive blades, and low-priced printers that then require repeated purchases of expensive ink cartridges. The fundamental idea is to get a customer to try something so that they will be "hooked" into spending more in the future. This is what is commonly indicated by use of the term "starter product."

But the authors' use of the term "starter product" does not fit with this ordinary understanding of the term, indicating a subtle attempt to mislead. In the context of the article, the term implies that youth might try menthol cigarettes before non-menthol because they are easier to smoke, and then get "hooked" into an addiction to either menthol or non-menthol cigarettes. However, the authors do not claim that their study shows that menthol cigarettes are part of a marketing strategy to get youths hooked. And menthol cigarettes are not a lower-priced or more basic type of cigarette. Early on in the article, the authors suggest that they are using "starter product" in its commonly understood meaning by stating that "[w]e ... examine the possibility that menthol cigarettes serve as a starter product to established smoking" [Emphasis added] However, at the end of the study, they state that the "association" indicated in their study" [presumably between a higher rate of menthol cigarette smoking by middle school vs. high school youths] "does not necessarily imply causality" and that the term "starter product" "is not necessarily the same as being a gateway product in terms of facilitating subsequent use." At 412. So, if the term does not mean what it usually means, what does it mean? All that can be gathered from the article is that "starter product" means that many youths who are starting to (or experimenting with) smoking have tried a menthol cigarette (it is "one of the most prevalent types used by younger, newer smokers" (emphasis added)). Should this be news, or the basis for drawing conclusions about whether some use of menthol cigarettes by youths indicates such use leads to habitual smoking in later years? Certainly not -- at least not under the IQA and its guidance, which require reliable data and unbiased analysis and presentation.

As for the actual numbers reported in the article, the unreliability of the underlying NYTS survey data used as the basis for the study is demonstrated by the numbers in Table 3 of the article. Over 900 of the 4294 members of the overall smoking group did not indicate whether they smoked menthol cigarettes or what brand they smoked. Since the survey did not ask about smoking of non-menthol cigarettes (just several non-menthol brands), a portion of these smokers were probably non-menthol smokers in the last 30 days, but were not included in the non-menthol group. Table I tells a similar tale: Included in the "menthol" group were a large number of "possible" menthol smokers because they indicated they smoked both menthol and non-menthol brands. Furthermore, on p. 407 (1st col.) of the article, it can be seen that a large proportion of the smokers apparently did not even know whether the cigarette they smoked was menthol or not, because they identified the brand they smoked as a menthol brand but did not identify themselves as menthol smokers.

Next, we look at the reliability of the Hersey *et al.* analysis leading to the conclusion (or implication), highlighted by FDA, that young smokers start smoking by smoking greater numbers of menthol cigarettes before moving on to non-menthol cigarettes.

Center for Regulatory Effectiveness

On this subject, we first note that the study considers a youth a menthol cigarette smoker if they smoked as few as one or two cigarettes in the last 30 days. Table 3 shows that more than half of the smokers classified as "menthol" smokers smoked between 1 and 19 cigarettes in the previous 30 days, but the numbers of cigarettes smoked are not broken down further. We also see from Table 3, as well as Table 1, that included in the "Menthol group" were smokers who indicated they smoked a menthol cigarette but then identified the brands they smoked as "mixed" (*i.e.*, both menthol and non-menthol). Since the survey did not ask whether a respondent had smoked both menthol and non-menthol cigarettes in the last 30 days, it is not possible to tell what portion of the "Menthol group" smoked both types.

In short, from the numbers, it appears that the "Menthol group" was substantially inflated, and that many of the young smokers could not tell the difference between menthol and non-menthol.¹⁸

This basic observation severely undercuts one of the basic "findings" of the Hersey *et al.* study: "Here we first document a recent increase in the use of menthol cigarettes." At 404 2d col. Given the uncertainties and inconsistencies explained above, the asserted "documentation" of any such increase is unreliable.

Finally, some of the basic mathematical calculations reported in the study are so inaccurate as to call the rest of the study into question. The authors state that between 2000 and 2002 "the percentage of smokers who regularly used menthol cigarettes increased significantly ... from 40.0% to 47.4 % -- an increase of 18.5 %." They also state that those who smoked a menthol brand, even if they did not recognize that it was menthol, saw a relative increase of 16.2% (from 43.2% in 2000 to 50.2% in 2002). Both of these increased percentages -- 18.5% and 16.2% -- are inaccurate and inflated. The percentage increase given would be accurate if the baseline were the lower percentage number; but the baseline from which the percentage increase should be calculated is the percentage of the subject menthol smoker population, not a subset. Thus, an increase in the total population from 39.0% to 46.2% is an increase of 7.2%, not 18.5%; and an increase from 43.2% of the total population to 50.2 % is an increase of 7.0%, not 16.2%. (This presumes, of course, that the numbers of menthol smokers were accurate, which, as discussed above, is very likely not the case.)¹⁹

On the topic of nicotine dependence in menthol vs. non-menthol smokers, the Hersey *et al.* study appears if anything even more unpersuasive and unreliable, although the authors make equivocal statements regarding the significance of their "findings." The authors state that their study "provides evidence that menthol cigarettes may be more difficult to quit." At 411. This

¹⁸ In fairness to the authors, although they report numbers with apparent precision, at one point in the article they actually state: "One possible explanation for the inconsistencies is that these youth had not smoked long enough to recognize and accurately report the type of cigarette they usually smoked. (Similarly, 61.7% of youth who did not identify either the brand or the menthol status of the cigarettes they usually smoked had smoked for less than 1 year.)" At 407 2d col. However, FDA did not note this obvious limitation/error source.

¹⁹ For example, if the total menthol population was 1,552, as shown in Table 3, a percentage increase of 40.0 to 47.4 would amount to a 115 person increase, which is a 7.4% increase, not an 18.5% increase.

Center for Regulatory Effectiveness

evidence is based on menthol smokers (who, as we have seen might not really have been menthol smokers) reporting less that they were "seriously thinking about quitting." On the other hand, as the article reports, menthol smokers were more likely to report that they attended cessation programs or used nicotine replacement products. This seems to be evidence that menthol smokers were more serious about succeeding in quitting, but the study does not mention this interpretation, and instead states that -- supposedly in support of increased dependence of menthol smokers -- that the menthol smokers (if they were that) were no more successful in quitting and that "menthol smokers" (again, if that's what they were) scored higher on a scale of nicotine dependence. Not only is the interpretation of the data suspicious and unreliable, but the numbers on which it is based are unreliable, as discussed above. After suggesting various factors that might account for the supposed higher nicotine dependence of menthol smokers, the authors state that this area of their study "can benefit from further investigation" and "further investigation of the role of mentholated cigarettes deserves close attention."

On the subject of dependence, the study also presented a finding that "teens" (*i.e.*, those in middle school and high school -- actually not all teens because some would have been between the ages of 11 and 18-- scored 45% higher on the Nicotine Dependence Scale for Adolescents. However, the study did not note that previous studies of adult menthol smokers using the Fagerstrom scale did not show any difference,²⁰ and no explanation was offered for why adolescents might differ from adults in degree of dependence. The difference in results between the Fagerstrom scale and the NDSA scale could easily be explained by the weighting of questions. The Fagerstrom questionnaire has six questions, and only one asks about smoking within the first sixty minutes after waking. However, the NDSA, which also has six questions (set out in Table 2 of the Hersey *et al.* study) asks two questions about smoking after waking up, and is not specific with regard to how the answer will be scored. If in fact youth menthol smokers smoke their first cigarette sooner after waking, it is possible that the NDSA would therefore weight that factor more heavily than the Fagerstrom scale, with the result that the NDSA would show greater dependence. But does a tendency of menthol smokers to have their first smoke sooner after waking really even show a greater degree of dependence? Other tests for dependence such as quit ratios and the Fagerstrom scale do not so indicate. And a tendency of menthol smokers to smoke sooner after waking could be explained simply by the taste of menthol cigarettes being regarded by the smoker as a mild antidote to "morning mouth," in much the way menthol/peppermint is added to toothpaste and mouthwash to give them a more refreshing taste. On this point, the Hersey *et al.* study does not attempt to explain why the results from the Fagerstrom test and the NDSA should be different, and how the NDSA was scored, and instead presents an overly simplistic and apparently biased picture.

In summary, the Hersey *et al.* study and the NYTS data are simply too unreliable (and

²⁰ A related FDA slide shown by Hoffman, No. 13, stated that a study by Collins and Moolchan, 2006, found that "[m]enthol smokers had **shorter** TTFC" (Original emphasis; TTFC is an acronym for time to first cigarette). However, the slide also presents a figure that shows how fragile such findings are, because menthol smokers exceeded non-menthol smokers only in the first five minutes after waking, and non-menthol smokers exceeded menthol smokers between 6 and 60 minutes and after 60 minutes. Thus, such results could turn simply on survey respondents' subjective estimates of whether they smoked within five minutes after waking or slightly more than five minutes, and when they had actually "awakened" (*e.g.*, opening their eyes vs. getting out of bed and walking around).

Center for Regulatory Effectiveness

possibly biased) on which to base any conclusions, and any agency or TPSAC conclusions based on those data would therefore also be unreliable and not in compliance with IQA standards. After considering the above discussion, it is interesting to go back and read the abstract of the study. The abstract indicates significant bias, particularly when compared to the full text of the study report.²¹ See additional [analyses](#) .

b. Accuracy and objectivity of the Rising/FDA presentation of the Hersey *et al.* study findings

Although Dr. Rising did not give much significance to the Hersey *et al.* numbers for a decrease in menthol smoking between middle school and high school, he does take them at face value as being accurate and reliable, which they are not. No limitation or error sources are described or even indicated. Also, by singling out those particular numbers for an agency presentation on smoking initiation, he indicates they have some significance as indicating that menthol smoking contributes to initiation, which cannot be the case if the numbers are inaccurate and unreliable. Finally, he indicates that the significance of the numbers could be to indicate individuals "transitioning from menthol cigarettes to nonmenthol cigarettes," an inference that is not only unsupported by reliable numbers but one that is disavowed in the study report.

c. Accuracy and objectivity of the Hoffman/FDA presentation of the Hersey *et al.* study findings

Dr. Hoffman presented a slide and comments based on the Hersey *et al.* study that were notably ambiguous on the subject of menthol smoking and cessation in youth. The slide (No 15) states that there is "No information on quitting success comparing menthol to non-menthol youth smokers." But then, citing the Hersey *et al.* study, the slide states that the study showed that youth menthol smokers were less likely to be "seriously thinking about quitting," and that you menthol smokers were more likely to have sought help in quitting.

Obviously, there is a lot of inconsistency or room for interpretation in such statements, not to mention that the underlying statistics in the study for numbers of menthol vs. non-menthol are unreliable, as discussed above. If there is "no information," why is the Hersey *et al.* study of any significance? If youth menthol smokers are less serious about quitting, as implied, why would they be more likely to seek help that could make their quit attempt more likely to succeed? Also, there is the unspoken question of why any youth who has smoked just one or a few menthol cigarettes in the last 30 days would think it necessary to be concerned about quitting.

In her comments on the slide, Dr. Hoffman made an inaccurate and biased interpretation of the Hersey *et al.* findings indicated on the slide. The study indicated that youth menthol smokers were overall more likely to seek help in quitting; however, Dr. Hoffman converted this into the statement that those youth menthol smokers "who did try to quit" -- which would be a subgroup of the menthol group -- were more likely (apparently than non-menthol smokers trying to quit) to have sought assistance. This is a distortion of the study and appears intended to give

²¹ The authors were all with the American Legacy Foundation, the declared mission of which is the reduction and eventual eradication of smoking.

the impression that menthol smokers trying to quit have a more difficult time quitting because they seek help. An additional distortion is that neither the slide nor Dr. Hoffman's comments on it provide the information from the study that there was no difference between menthol smokers and non-menthol smokers in trying one or more times to quit.

2. Okuyemi KS *et al.* 2003 Does menthol attenuate the effect of bupropion among African American smokers? *Addiction* 98:1387-93.

The Hoffman/FDA slide presentation on menthol and smoking cessation at the March 30-31 TPSAC public meeting included two slides (Nos. 7 and 9) citing this study. Both the slides and Dr. Hoffman's comments of the slides (Tr. at 210, 217) state that adult menthol smokers have less success in quitting while using pharmacotherapy and counseling than non-menthol smokers, particularly when using bupropion SR (Zyban). (Side # 7 is more specific to the Okuyemi *et al.* 2003 study.)

As with the Hersey *et al.* study, *supra*, FDA dissemination of this information raises two distinct but related IQA issues: (1) Was the Okuyemi *et al.* 2003 study a sufficiently reliable source for such FDA conclusions; and (2) Did Dr. Hoffman and FDA accurately present the study and its limitations?

a. Reliability of the Okuyemi *et al.* 2003 study

This study compared two groups of African-American smokers -- menthol and non-menthol -- for success in quitting after 7 weeks of treatment with the drug bupropion SR. The authors concluded that at six weeks after beginning a 7-week treatment period with bupropion, menthol smokers were significantly less likely (28% menthol vs. 42% non-menthol) to have been abstinent for seven days. However, at six months after start of treatment, the difference was not statistically significant (21% menthol vs. 27% nonmenthol).

Although the study compared these two groups, a prominent feature of the study is that the groups were not comparable. The menthol group contained 471 subjects, while the non-menthol group contained only 129 subjects. How this disparity was handled in calculating the percentages of cessation is not explained. The small size of the non-menthol group provides lower statistical confidence, and the size disparity could have amplified other differences between the groups. In particular, the menthol smokers were significantly younger and more likely to be female. The age difference is of particular importance, but did not receive emphasis by the authors. They noted that it is well-recognized that age is associated with cessation success (positively -- more success in quitting at higher age), that the (much smaller) non-menthol group was older, and they included a figure (Fig. 2) and narrative showing that at six weeks, menthol smokers over 50 yr. were showing more success with cessation. This would mean that if the menthol group had been older, it would have been more likely to have had a higher level of success in comparison to the non-menthol group. The greater number of females in the menthol group could have significantly affected the results also, because it has been established that women are less successful at quitting than men, for a variety of reasons.²²

²² See, e.g., The 2001 SURGEON GENERAL'S REPORT ON WOMEN AND SMOKING, at 549 *et seq.*, and Wetter DV *et al.* 1999. Gender differences in smoking cessation. *J Consult Clin Psychol* 67(4):555-62.

Center for Regulatory Effectiveness

Despite these problems with the study, the authors did not concede that the size disparity between the groups was a significant limitation on the accuracy of the reported quantitative cessation results. Instead, they only stated that "having a large sample of non-menthol smokers in the study is unlikely to change factors that were found to be significant in this study." (Emphasis added) In the discussion of limitations, the age differences between the two groups received no attention, despite the authors' recognition of its significance earlier in the study report. Moreover, the authors were at a loss to explain the strong trend towards greater success among menthol smokers at six months in comparison to six weeks.

This study also raises, but does not attempt to answer, the question of whether a cessation period of seven days is a reliable indicator of successful cessation. Just from the disparity in results between six weeks and six months, one would conclude that such a short period of abstinence is not a reliable indicator.

On the whole, the study is interesting but has a very low level of reliability. The authors need to conduct another study with comparison menthol and non-menthol populations of similar large size and with matching characteristics, particularly in terms of age and gender. And the reasons for the changes in comparative success at six months vs. six weeks need more exploration, through interviews if by no other means.

In short, the unconventional and unexplained aspects of this study do not allow it to be generalized. It cannot be considered reliable and useful. See additional [analyses](#).

b. Accuracy and objectivity of the Hoffman presentation of the Okuyemi *et al.* study

The principal slide used by FDA/Hoffman (#7) stated, without any qualification, that the study showed that "Bupropion increases abstinence at 6 weeks" and that "Menthol smokers have significantly poorer outcomes with bupropion (interaction)." (Original emphasis) Dr. Hoffman's comments on the slide were similarly unqualified, stating flatly that "bupropion ... is less efficacious for menthol smokers." (Tr. at 210.) FDA/Hoffman did not show or discuss any of the factors effecting the reliability of the study discussed above. In particular, she gave no indication of, and did not discuss --

- the great disparity between the menthol and non-menthol group sizes, and how that could have affected the statistical results;
- the greatly differing results at six months vs. six weeks; or
- the age and gender differences between the groups and how they could have affected the findings.

As a result, the FDA/Hoffman characterization of this study cannot be considered objective and unbiased. If it had been, the significant weaknesses in the study would have been apparent.

3. Okuyemi KS *et al.* 2007 Relationship between menthol cigarettes and smoking cessation among African American light smokers. *Addiction* 102:1979-86.

At the March 30-31 TPSAC meeting, the FDA/Hoffman slide presentation on menthol smoking and cessation also highlighted this study (slides 9 and 17), and Dr. Hoffman commented on it at Tr. 211-12 and 217.

a. Reliability of the Okuyemi *et al.* 2007 study

This study used a database similar to the above 2003 study and that was also an offshoot, or re-analysis, of the primary clinical study. It differed mainly in that it studied cessation with combinations of nicotine replacement gum and either motivational or health counseling. However, it was similar in that the menthol group was vastly larger than the non-menthol group (615 vs. 138).

Although nicotine replacement gum and bupropion might appear significantly different, their basic mechanism is similar. Bupropion is generally considered an anti-depressant that operates mainly by increasing dopamine release by the brain. The mechanism for nicotine is similar in stimulating dopamine release. So one would expect fairly similar results.

The results shown by this study, however, are quite different from the 2003 study, above. The authors found no significant difference between menthol and non-menthol smokers at 8 weeks, which was the end of the therapy period; but they found higher, but non-significantly higher, quit rates for menthol smokers over non-menthol smokers (with the exception of the placebo plus motivational counseling group) 26 weeks after the start of intervention. The only explanation the authors could offer for this apparent anomaly was that the primary clinical study from which it was derived also did not show an effect of nicotine gum over placebo at 8 weeks.²³ However, that is not really an explanation, since the primary study did not separate menthol smokers from non-menthol smokers.

Another prominent anomaly in this study is in the lack of coherence between the effects shown with different combinations of treatment. As shown in Figure 3, there was essentially no difference in menthol vs. non-menthol cessation at 26 weeks from the combination of placebo plus motivational counseling. However, there was a substantial increase in non-menthol cessation vs. menthol cessation from placebo plus health education. This is clearly inconsistent with Figure 2, which shows a substantial increase in non-menthol cessation at 26 weeks from both placebo and motivational counseling. Based on Figure 2, one would expect an even more substantial increase in non-menthol cessation over menthol cessation from a combination of placebo plus motivation counseling, contrary to the findings reflected in Figure 3. One likely explanation for this incongruity is simply the size disparity of the menthol and non-menthol comparison groups, which could amplify any factorial disparity between the groups, such as the age disparity or the confidence-in-quitting disparity.

The main finding from this study, therefore (if any), is not really the effect of menthol vs. non-menthol on the effectiveness of pharmacotherapy, but a more consistent effect of both

²³ Ahluwalia JS *et al.* 2006. *Addiction* 101:883-91.

Center for Regulatory Effectiveness

motivation and health counseling on improving non-menthol quit ratios. The reason for this effect cannot be analyzed from the data in the study.

In general, though, this study again illustrates the problems with trying to conduct a statistical analysis using comparison groups of very disparate size and composition, with the smaller group being so small as to be very susceptible to random or non-quantifiable variables, or amplifying slight variables such as age or confidence in quitting. See additional [analyses](#).

b. Accuracy and objectivity of the Hoffman/FDA presentation of the Okuyemi *et al.* 2007 study

The FDA/Hoffman slides simplistically indicated that lower cessation rates for non-menthol smokers in the study were due solely to menthol, and did not show the lack of an effect at the end of treatment (8 weeks) or the incongruous results from comparing the lack of a placebo effect along with motivational counseling to other data showing increases in cessation in non-menthol smokers from both placebo and health counseling.

The FDA/Hoffman slides also do not give any indication of the great size disparity between the menthol and non-menthol comparison groups and how this might have affected, or limited the usefulness of, the study findings. Instead, the slides provide only the stark message that "menthol smokers have **lower** levels of abstinence/successful quitting." (Hoffman slide #17, original emphasis.)

Dr. Hoffman's comments on this study were as simplistic as the slides. There was no discussion whatever of the limitations and incongruities in the study -- instead only a brief description and the unqualified statement that this study showed that "cessation success was reduced by menthol." (Tr. at 212.)

Such a simplistic presentation does not meet IQA standards because it is incomplete with regard to describing the problems with "error sources" and the limitations and inconsistencies evident in the study report.

4. Harris KJ *et al.* 2004. Predictors of smoking cessation among African-Americans enrolled in a randomized controlled trial of bupropion. *Prev Med* 38:498-502.

The FDA/Hoffman slide presentation on menthol cigarettes and smoking cessation at the March 30-31 TPSAC meeting also emphasized this study (slides 8 and 17). Dr. Hoffman described the study at Tr. 210-11, but described only the menthol smoker portion of this multivariate study.

a. Reliability of the Harris *et al.* 2007 study

This study used the same primary database and study populations as the Okuyemi *et al.* 2003 study discussed above, and calculated the effect of menthol smoking in the groups as in the prior study.²⁴ The only difference was that it attempted to look at many factors in addition to

²⁴ Dr. Okuyemi was also one of the authors of this study. Other authors were from the same universities

menthol smoking that might have influenced the cessation outcomes. The reported numbers for menthol smoking and its impact on cessation, and the parameters (7 days cessation at end of 7 weeks) were exactly the same. Likewise the limitations described with regard to the Okuyemi *et al.* 2003 study are the same: a highly disparate comparison group size, with the non-menthol group being far smaller (129 vs, 471 menthol); lack of comparability in potential influencing factors such as gender and age between the menthol and non-menthol groups, due in large part to the primary study not having been designed to look at the effects of menthol smoking; and a cessation window of very questionable validity. Unlike the prior study, however, this study did not report on the change in cessation results between seven weeks and six months.

b. Accuracy and objectivity of the FDA/Hoffman presentation

Although Dr. Hoffman gave what appeared to be an essentially objective description of this study, she did not tell the committee that the menthol portion was essentially the same as in the Okuyemi 2003 study that she had just finished describing, and she gave the impression that it was an additional study rather than essentially a duplicate. Dr. Hoffman even appeared to try to mask this duplication by describing the Okuyemi *et al.* 2003 study as having 600 smokers, and the Harris *et al.* 2003 study as having 535 smokers. In reality the number of smokers included in the calculations (535) was the same, and the 600 smoker number was the number of smokers at the start of the study, not at the seven-weeks-of-treatment calculation point.

The Harris *et al.* 2004 study does not appear to add anything new with regard to the calculated potential effect of menthol smoking on the efficaciousness of bupropion in this study group. It's inclusion in the FDA slide presentation on menthol smoking and cessation without describing it as essentially a duplication of Okuyemi *et al.* 2003 -- whether intentional or not -- biased the weight of the evidence presented to the TPSAC and the public. Additional [analyses](#)

5. Kreslake JM *et al.* 2008. Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults. *Am J Pub Hlth* 98(9):1685-92.

The FDA/Rising slide presentation on consumer perceptions of menthol cigarettes at the March 30-21 TPSAC meeting contained a slide that quoted this study as stating that "[w]e found evidence that the tobacco industry ... introduced new menthol brands to gain market share, particularly among adolescents and young adults." (Slide 39, emphasis added) Dr. Rising commented in his verbal presentation that this quotation was a conclusion from the Kreslake *et al.* review of industry documents. (Tr. at 164-65) This slide and Dr. Rising's comments were made in a portion of his presentation addressing "marketing of cigarettes to youth and young adults" and the role of advertising in "the initiation of smoking." (Tr. at 159) FDA/Rising also quoted from the Kreslake *et al.* study in the presentation on menthol cigarettes and smoking initiation. Slide 20 repeated a quotation obtained by Kreslake *et al.* from industry documents that "[f]irst-time smoker reaction is generally negative ... Initial negatives can be alleviated with a low level of menthol."

a. Accuracy and objectivity of the Kreslake *et al.* 2008 study.²⁵

in both publications. It is noteworthy that the authors did not mention menthol in the title.

²⁵ There is another Kreslake *et al.* 2008 study, not addressed here, titled "The menthol smoker: tobacco

Center for Regulatory Effectiveness

As explained below, this study is clearly inaccurate and biased in the above study conclusion quoted by Dr. Rising and also in other stated conclusions from the study with regard to any industry focus on "adolescents." In the Conclusions section of the study report, the authors state:

For decades, tobacco manufacturers have controlled levels of menthol in commercial cigarettes to promote smoking among adolescents and young adults. Manufacturers have marketed brands to this vulnerable population by manipulating sensory elements of cigarettes to promote initiation and dependence.

At 1689 (emphasis added). Also, the title of the study report emphasizes adolescents: "Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults." The study report also states in the abstract that the industry has used a menthol strategy "in attracting youth and young adult smokers."

A careful review of the study report and the key company documents that it quotes provides no evidence for "targeting" or "marketing" to "adolescents" or "youth" (as opposed to "young adult smokers"). There is a clear distinction, evident in the article and in common language, between "adolescents" and "young adults." "Adolescents" are not adults (or "young adults"); they are generally regarded as youth on their way to becoming adults, roughly between puberty and adulthood, and defined by Merriam-Webster as youth between puberty and the age of majority. The age of majority is 18 in all but three States (19 in two, and 21 in one). "Young adults" are commonly defined throughout the industry as between the ages of 18 and 24 -- an age which is the legal age for smoking in all but three States (as with "age of majority").

The industry documents referenced and quoted in the Kreslake *et al.* study do not refer to adolescents or smokers under the age of 18 as marketing targets in any respect. The industry documents relied on in the study refer only to "young adult smokers" (abbreviated as YAS). The Kreslake *et al.* statements regarding targeting of adolescents or youths (vs. young adults) is inaccurate and appears to be intentionally inflammatory and biased. The study also appears to be biased in its interpretation of the term "first-time smoker" in Rising slide # 20 on initiation. The industry document from which this quotation was taken was, when read in full, a document about marketing to "young adult smokers" (*i.e.*, between 18 and 24), and the reference in the article to "first-time smoker" in the context of conclusions about targeting of "adolescents" gives the impression that the industry document was about marketing to adolescents (which it was not) for the purpose of obtaining "initiation." In addition, the quotation was taken from a brief list of talking points for a pitch of a new idea to one company official, so it can hardly be referred to evidence of an "industry" activity.

On the whole, all the Kreslake *et al.* study shows is that there was some industry recognition that some young adult smokers appeared to prefer certain levels of menthol as opposed to older smokers. There is nothing in the study to support a conclusion that the industry

industry research on consumer sensory perception of menthol cigarettes and its role in smoking behavior," which is referenced in Dr. Rising's slide 35 as part of his presentation on consumer perceptions of menthol cigarettes.

Center for Regulatory Effectiveness

was using menthol to "target" "adolescents." Thus, on the whole, the article appears to be inaccurate and strongly biased -- and apparently an intentional attempt to mislead and inflame in order to support the authors' stated policy position on federal regulation. Additional [analyses](#).

b. Accuracy and objectivity of the Rising/FDA presentation of the Kreslake *et al.* 2008 study.

The best that can be said of the Rising/FDA presentation of the study is that it accurately represented the study's conclusions. However, agencies have an obligation to subject the studies and data they use to pre-dissemination review, and not take them at face value. Rising/FDA did not do this. If they had examined the study critically, they would have found that its conclusion about targeting of adolescents were unfounded and biased. In relying on the study, the agency presentation was also infected with the study's inaccuracy and bias. The agency also should have noted that the quotation about "first-time smokers" in initiation slide #20 was not really evidence of an industry position, but was simply taken from a brief set of talking points for a presentation of a marketing idea. This was a failure by the agency to provide context and completeness to the information, which are aspects of a failure of objectivity under the IQA guidelines.

6. Sidney S *et al.* 1989. Mentholated cigarette use among multiphasic examinees, 1979-86 *Am J Pub Hlth* 79(10):1415-16.

The FDA/Rising slide presentation on menthol cigarettes and smoking initiation included calculations on switching between menthol and non-menthol cigarettes in a large smoker cohort. The slide showed that 14.6 percent of 1,688 Black smokers switched from non-menthol to menthol cigarettes, and 3.6 percent switched from menthol to non-menthol cigarettes. Dr. Rising presented these figures without any additional comment. (Tr. 193-94)

a. Utility and reliability of the Sidney *et al.* 1989 study

This study is very old in the context of the issues being addressed -- almost 25 years old - - and during that period there have been substantial changes in the menthol cigarette market. The study is also very brief and provides very little detail on the age patterns related to the switching figures. The study attributes a recognized sharp decline in menthol cigarette use in relation to age to a "cohort effect" (*i.e.*, smokers of different ages could have been affected by different market conditions during the time they were smokers), but the possibility of a cohort effect in relation to switching is not discussed. See additional [analyses](#).

b. Utility and objectivity of the FDA presentations on initiation and cessation

An immediate question that arises with regard to presentation of these study calculations is what relevance such figures on switching have to smoking initiation. Apparently all the switchers were current smokers, so the implication seems to be that switching is somehow related to more Blacks initiating smoking. But any connection between switching and initiation is left unexplained. In the absence of an explanation, one might well deduce that since more Blacks were switching from non-menthol to menthol, there must have been a higher rate of Blacks initiating smoking with non-menthol cigarettes, and then switching to menthol.

Center for Regulatory Effectiveness

However, this implication is not discussed, which raises questions about whether the study was presented in a useful and objective manner in the context of the issue of initiation.

The study does contain some interesting information on smoking cessation -- finding that there was no significant difference between menthol smokers and non-menthol smokers in quitting (cessation) -- but Dr. Hoffman's FDA slide presentation on menthol smoking and cessation behavior does not mention this study, which is at odds with the IQA quality standards of completeness and objectivity.

7. Gandhi KK *et al.* 2009. Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic. *J Clin Pract* 63(3):360-67.

This study was also given attention in the FDA/Hoffman slide presentation on menthol cigarettes and smoking cessation at the March 30-31 TPSAC meeting. (Slides 13 and 18). Dr. Hoffman described the study at Tr. 214.

a. Reliability of the Gandhi *et al.* 2009 study

This study is very problematical. It has numerous limitations, some of which are indicated by the authors and others of which are discernible from the study report. Despite the categorical sound of the study title, the authors stated that the study only suggests that menthol cigarettes may increase addiction and make it harder to quit. Some of the reasons for this caution are explained below.

First, as in many of the other studies presented to the TPSAC, the studies were not designed with similar comparison groups. The study subjects here were not selected, they were self-selected by seeking quit assistance at a clinic. As a result, the study group was very diverse virtually all relevant respects: race, age, gender, socio-economic status ("SES"), type/brand of cigarettes smoked, number smoked per day, etc. The authors seem to feel that this complexity was completely accounted for by statistical manipulation (logistic regression analysis with some of these factors "adjusted for" as covariates), but the ability of the statistical model(s) to deal with this level of complexity is very doubtful. For example, where did the values for the covariate adjustment factors come from? How accurate are they? Was the sample size large enough to allow for sufficient covariate adjustments? Out of the 1688 subjects, only 27 showed up in person for the six-months follow-up, and the rest (number not given) were interviewed by phone without any validation by measurement of CO in breath.

As in other studies, this great disparity in comparison groups could have amplified confounding factors. The authors state that the menthol group of AA (African American) smokers was younger, had more females, was less educated, and less likely to be married. Table 1 shows that they were also less employed. All of these factors could have skewed the results in the direction of less menthol quitting, particularly when we see that the AA group was comprised of 302 menthol smokers and only 72 non-menthol smokers, while the White smoker group was comprised of 348 menthol smokers and 738 non-menthol smokers.

Center for Regulatory Effectiveness

Other aspects of the study simply lack transparency on relevant factors. Although many of the participants apparently made use of pharmacotherapy, no numbers or breakdowns by age, gender, etc. are given. And, although the groups are categorized as menthol and non-menthol, there is no information given on whether any effort was made to validate whether the classifications were accurate based on brand, or whether some might have smoked both types.

The authors conceded that they could not assess SES "in a comprehensive manner" (365) and that therefore "[t]he results from this clinic may not be generalized to other tobacco treatment situations."

Finally, as with some of the other cessation studies, the authors used a seven-day cessation period as a measure of cessation. The relevance of such a measure is extremely doubtful. See additional [analyses](#).

b. Objectivity of the FDA/Hoffman presentation of the Gandhi *et al.* 2009 study

The two slide presentations of the study emphasized that Black smokers "did worse at 6 months" and that the study showed a "significant" interaction between race and menthol smoking with regard to cessation (slide 13), although the second slide (# 13) referred to a "possible" interaction between race and menthol. Dr. Hoffman's verbal presentation accompanying the slides emphasized that "Black menthol smokers did worse when you look at the six month outcome." (Tr. 214). There was no information given, or discussion of, the limitations of the study or the cautionary statement of the authors that the results should not be generalized to other clinic situations. The FDA/Hoffman unqualified statements regarding Black cessation results at six months are particularly troublesome given the small size of the Black non-menthol group (n=72) and the fact that there were overall so few in-person follow-ups (n=27, both menthol and non-menthol) at six months, without any further breakdown of follow-ups by race.

Presenting the study as supporting unqualified findings, without any discussion of its many limitations, is a clear violation of the IQA objectivity standards, which require completeness and discussion of error sources/limitations.

8. Pletcher MJ *et al.* 2006. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function. *Arch Intern Med* 166:1915-22.

Although this study was highlighted in both the initiation (slide 11) and cessation (slides 12 and 16) FDA slide presentations, the findings presented in those slides indicated no difference between menthol and nonmenthol smokers' cessation success or health effects. However, following the presentation, the committee members asked clarifying questions about the various studies, and one that was significant with regard to this study was posed by TPSAC member Dr. Benowitz. Dr. Benowitz was a co-author of the Pletcher *et al.* study, and he stated that one of the "really interesting findings" of the study (not shown in the slides) was "an effect of menthol on relapse." (Tr. at 228). If this were the case, he said, it would mean "that fewer people are quitting permanently," and he wondered whether other databases had information on relapse. The question here, therefore, is whether Dr. Benowitz was correct in indicating that the Pletcher *et al.* study showed more relapse among menthol smokers, and therefore less success in

Center for Regulatory Effectiveness

achieving cessation, and if it did, whether those study findings are sufficiently reliable to satisfy IQA standards.

The study defined relapse as "baseline smokers who reported no current smoking at a subsequent examination and then current smoking the final time they were examined." At 1916. The study found that, based on this metric, menthol smokers had a significant increase in the risk of relapse.

Based on the definition of relapse in the study, however, those findings of greater risk of relapse among menthol smokers cannot be considered even fairly reliable. Relapse was determined only at the final examination, with four intervening examinations after baseline, at each of which a subject could have reported that they were either currently smoking or not smoking. Thus, a menthol subject reporting current smoking at the final examination might have had only one relapse (and that for a minimal amount of time coinciding with the final examination), while a non-menthol smoker could have been counted as having had zero relapses based on not currently smoking at the time of the final examination, although they had in fact also relapsed before the final examination. The tables below illustrate this scenario.

Hypothetical Menthol Subject Relapse Example -- One Relapse Counted

Measures	Baseline	Years after baseline				
currently smoking: yes/no	1985	2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
smoking status (1=yes; 0=no)	1	1	1	0	0	1

Hypothetical Nonmenthol Subject Non-relapse Example -- No Relapses Counted

Measures	Baseline	Years after baseline				
currently smoking: yes/no	1985	2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
smoking status (1=yes; 0=no)	1	0	0	1	1	0

As can be seen, using the study metrics, a menthol subject could have been counted as having a single relapse, while a nonmenthol smoker could have been counted as having no relapses, even though that nonmenthol smoker had actually had a relapse. In addition, it appears likely that this unreliable metric was biased towards more menthol smoker relapses because it was determined that menthol was associated with a lower likelihood of trying to quit in the first place, increasing the likelihood of fewer quit/relapse occurrences before the final examination among menthol smokers. (At 1917) While the examples in the tables could also be reversed between menthol and nonmenthol, and other sequences of yes and no at the time intervals could be used, the point is that the metric used by the study for determining relapse rates was not reliable.

As the study authors also point out, the relationship between menthol smoking and ethnicity introduced uncertainty into the quit findings. They state: "These findings suggest that menthol cigarettes may be harder to quit smoking, but uncertainty about this point remains, in part because of the difficulty and large sample sizes required to tease apart the effects of ethnicity and menthol preference, which are highly correlated." (At 1918) The same could also

Center for Regulatory Effectiveness

be said for the consistent correlation between menthol preference and gender, as shown in Table 1 (55% menthol, 48% nonmenthol among women) and in other studies, with females recognized as experiencing lower quit rates. In other words, quit or relapse rates for menthol cigarettes could be more a result of cultural or gender factors than a result of the menthol itself.

Thus, this is an illustration of a study that might be considered reliable on some points, such as health effects, but cannot be considered reliable on others, such as risk of relapse. Because the Benowitz comments on relapse rates were not countered or questioned by the presenting FDA/CTP officials, they appear to be acknowledged as accurate and reliable. See additional [analyses](#).

IQA Quality Issues Likely To Be Pertinent to Other Menthol Cigarette Studies as Illustrated by the Above Examples

In all of the eight examples of studies and FDA presentations reviewed above for IQA quality standards compliance, there were significant deficiencies in the studies, the FDA presentation, or both. This suggests that there are likely to be similar deficiencies in many of the other studies considered by the TPSAC or in the FDA presentation of those other studies. Therefore, attention should be given to ensuring that the following types of deficiencies identified above are not repeated, and that studies relied on by FDA, and FDA characterization of those studies, include:

- Disclosure and explanation of limitations/uncertainties and within-study inconsistencies;
- Consideration of plausible alternative explanations for observed results;
- Completeness in describing the results and in describing results from other competent studies that are inconsistent;
- Careful consideration and characterization of the reliability of the study design and methodology, and the reliability of study conclusions, recognizing that some study conclusions might have a higher degree of reliability than others;
- Transparency with regard to methodology, including any adjustments made for significant covariates/confounders;
- Consideration of the making generalizations of the study results.

Consideration of these points will be important as the TPSAC continues its work, and as FDA and continues to present its views on the scientific evidence to the committee and the public.

Corrections Needed

Corrective action is required to mitigate two types of harm resulting from the FDA disseminations of the slide presentations, the accompanying verbal comments in the transcript,

Center for Regulatory Effectiveness

the recording of the webcast, and the third-party studies relied on by FDA/CTP in those presentations.

1. Harm to the TPSAC's deliberations resulting from the committee having been provided with, and directed to discuss studies not meeting IQA quality standards, and not being given an objective and unbiased discussion of the relevant literature. Unless corrected, this non-compliant information could result in the committee making their recommendations on menthol on the basis of flawed information that is not IQA-compliant.
2. Harm to all stakeholders and members of the public interested in the menthol issue from a scientific and/or public policy perspective. The public counts on materials presented on the FDA's website being of the highest quality. Poor quality information on the agency's website can misinform countless personal and public decisions.

Each of the above types of harm requires a separate corrective action by FDA, as described below.

- **Corrective Action for TPSAC Harm:** The FDA should inform the TPSAC at their next public meeting that the FDA slide and verbal presentations, and the studies on which they are based, discussed herein do not meet IQA quality standards. Those studies, discussed above, include:

Hersey JC *et al.* 2006 Are menthol cigarettes a starter product for youth? *Nicotine & Tob Res* 8(3):403-13.

Okuyemi KS *et al.* 2003 Does menthol attenuate the effect of bupropion among African American smokers? *Addiction* 98:1387-93.

Okuyemi KS *et al.* 2007 Relationship between menthol cigarettes and smoking cessation among African American light smokers. *Addiction* 102:1979-86.

Harris KJ *et al.* 2004. Predictors of smoking cessation among African-Americans enrolled in a randomized controlled trial of bupropion. *Prev Med* 38:498-502.

Kreslake JM *et al.* 2008. Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults. *Am J Pub Hlth* 98(9):1685-92.

Sidney S *et al.* 1989. Mentholated cigarette use among multiphasic examinees, 1979-86 *Am J Pub Hlth* 79(10):1415-16.

Gandhi KK *et al.* 2009. Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic. *J Clin Pract* 63(3):360-67.

Center for Regulatory Effectiveness

Pletcher MJ *et al.* 2006. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function. *Arch Intern Med* 166:1915-22.

Although the TPSAC is free to utilize whatever studies it chooses in deciding what to recommend to FDA with regard to menthol cigarettes, unless their recommendations and the scientific evidence in studies relied on in their analysis comply with all applicable IQA quality standards, the FDA will not be able to rely on the TPSAC recommendations.

For your convenience, attached herewith are (1) copies of the studies we reviewed, and (2) a copy of the report on each of the aforementioned studies produced by our statisticians.

- **Corrective Action for Stakeholder and Public Harm:** The FDA should 1) place a prominent note on its website where the March 30 meeting slides and transcript and recorded webcast are being disseminated stating that the information on the scientific literature contained therein and the studies on which that information is based do not meet FDA quality standards, and 2) place a similar note on the pdf files of slides, transcript, and the webcast recording.

As explained at the outset of this petition, OMB has required that agency materials submitted to a committee for peer review purposes display a disclaimer that the materials are being disseminated for peer review purposes only and do not represent an agency position. Adding such a disclaimer at this late date, however, would not be an adequate remedy. The materials (FDA slides, verbal presentations, and recording of the webcast) have already been presented to the TPSAC, and have been disseminated to the public for a substantial period of time, without such a disclaimer, so that the harm associated with dissemination without the disclaimer must be redressed by the additional corrective actions requested herein.

How CRE Is Affected by the Non-Compliance

CRE is a regulatory watchdog established by former senior career officials from the Office of Management and Budget for the purpose of improving the transparency and accountability of the regulatory process. Since FACA committees inform many regulatory decisions, CRE established the FACA Under Fire website¹² to advocate for the independence and openness of FACA committees. The website is part of CRE's extensive support for the FACA process which has included participation in FACA meetings held by numerous agencies, including service by a CRE official on a FACA committee.

With respect to the TPSAC, CRE has taken its support for FACA independence a step further by establishing the TPSAC Interactive Public Docket ("IPD") to promote transparency and public participation in the committee's work, while acting as a vigorous watchdog over the proceedings with a particular focus on the FDA's actions vis-a-vis the committee.

¹² <http://www.facaunderfire.org/>.

Center for Regulatory Effectiveness

In addition to engaging in FACA-related activities, CRE works to improve the quality of the information used in federal proceedings and disseminated to the public. Although CRE is a long-standing advocate of the IQA correction process, the administrative and, if necessary, judicial processes initiated by filing an RfC are serious steps not to be taken lightly. For this reason, CRE invokes the correction process sparingly. Moreover, the development of substantive RfCs is a resource-intensive exercise. Information disseminations by the FDA with respect to the TPSAC that do not comply with the OMB and HHS/FDA IQA quality standards and require CRE's intervention result in the wasteful expenditure of CRE's resources.

Contact Information

The contact person for this petition is the undersigned. I can be reached at the address and phone number on the letterhead, or via email at tozzi@thecre.com.

We look forward to receiving a response to this petition not later than November 20 as required by the HHS and FDA IQA guidelines.

Sincerely,

/s/

Jim J. Tozzi
Member, CRE Advisory Board

cc: Jonathan Samet, M.D., Chair, TPSAC