



April 5, 2022

Mr. Mitchell Zeller
Director, Center for Tobacco Products
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD. 20993-0002

RE: FDA consideration of premarket authorization of menthol-flavored e-cigarette products

Dear Director Zeller:

The undersigned organizations write to express our concern that FDA has yet to issue any decisions on applications for marketing orders for menthol-flavored e-cigarettes or e-liquid products (collectively referred to here as “e-cigarettes” or “ENDS”). We believe granting any such orders would be inconsistent with the agency’s marketing denial orders (MDOs) for other non-tobacco flavored products and would be harmful to public health, particularly to the health of young people.

Our concern is prompted by FDA’s repeated failure to act on Premarket Tobacco Product Applications (PMTAs) submitted for menthol-flavored e-cigarette products at the same time it has, quite justifiably, issued MDOs for other flavored products. When FDA issued its first MDOs for e-cigarettes in August of last year, it expressed the view that the scientific review of menthol products “raises unique considerations.”¹ Most recently, in your remarks to the annual meeting of the Society for Research on Nicotine and Tobacco (SRNT), you stated that menthol e-cigarette products raise “unique considerations” in premarket review “due to the ongoing availability of menthol cigarettes.”²

¹ FDA News Release, *FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health* (Aug. 26, 2021), <https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-applications-about-55000-flavored-e-cigarette-products-failing-provide-evidence>.

² Mitchell Zeller, Dir., Ctr. for Tobacco Prods., FDA, Address at 2022 SRNT FDA Special Session, at 14:51-15:06 (Mar. 15, 2022), <https://www.youtube.com/watch?v=NVvYI-luA4M>.

Setting aside FDA's stated intention to issue a rule prohibiting menthol as a characterizing flavor in cigarettes,³ your statement suggests that FDA may be considering authorizing menthol-flavored e-cigarettes because of the presence of menthol cigarettes on the market. As explained below, however, given the strong appeal of menthol e-cigarettes to youth, and the absence of strong evidence of any countervailing benefit from these products in helping smokers stop smoking, any decision to authorize a menthol-flavored e-cigarette would be inconsistent with the approach FDA has taken in denying marketing orders for other flavored e-cigarette products and would fall far short of meeting the statutory standard of being appropriate for the protection of the public health (APPH),⁴ as that standard has been applied by the agency in the premarket review process.

FDA's Application of the Public Health Standard for Flavored E-cigarettes Other Than Menthol

In repeatedly denying marketing orders for flavored e-cigarette products because they do not meet the APPH standard, FDA's decision-making has adhered to a consistent principle: because flavored products have a demonstrated appeal to youth, an applicant must advance robust scientific evidence that the flavored product is effective in helping smokers stop smoking and that this benefit to smokers outweighs the well-established harm to youth. In its model Technical Project Lead (TPL) Review of PMTAs for e-cigarette products (Model TPL),⁵ which reflects the basis for every MDO issued for flavored products to date, FDA has explained its approach in this way:

Given the known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use, applicants would need reliable and robust evidence of a potential benefit to adult smokers that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.⁶

FDA has further elucidated the evidence that will be regarded as necessary to demonstrate a benefit of a flavored product to smokers:

...FDA has determined for these applications that to effectively demonstrate this benefit in terms of product use behavior, *only the strongest types of evidence will be sufficiently reliable and robust* – most likely product specific evidence from a randomized control trial (RCT) or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis. . .

³ FDA News Release, *FDA Commits to Evidence-Based Actions Aimed at Saving Lives and Preventing Future Generations of Smokers* (Apr. 29, 2021), <https://www.fda.gov/news-events/press-announcements/fda-commits-evidence-based-actions-aimed-saving-lives-and-preventing-future-generations-smokers>.

⁴ 21 U.S.C. § 387j(c)(2)(A).

⁵ <https://www.fda.gov/media/152504/download>.

⁶ Model TPL at 3.

Therefore, to demonstrate the potential benefit to current users, FDA has reviewed these applications for any acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.⁷

Applying this approach thus far, FDA has issued MDOs for every flavored product it has reviewed, finding that the applicants failed to produce reliable and robust evidence that their products confer a benefit on adult smokers sufficient to outweigh the demonstrated risk to youth. These conclusions are based on the best available evidence, which shows that flavored e-cigarettes attract youth, that the evidence is inadequate that e-cigarettes are effective at helping smokers to stop smoking, as well as the absence of solid scientific studies that flavors in e-cigarettes are necessary to help smokers stop smoking or benefit smokers to a degree that would offset the harm to youth and young adult non-smokers.

Application of the Public Health Standard to Menthol E-Cigarette Products

The MDOs issued thus far have not addressed menthol products or discussed whether menthol products are going to be categorized as “flavored” products for purposes of premarket review.⁸ But menthol is a flavor and there can be no doubt that menthol-flavored products present a “known and substantial risk” of “youth appeal, uptake and use.”⁹ When FDA restricted the sale of cartridge-based e-cigarettes in flavors other than menthol and tobacco in February, 2020, youth shifted to using menthol-flavored products.¹⁰ In 2020, over one million high school and middle school youth used menthol e-cigarettes.¹¹ According to the 2021 National Youth Tobacco Survey, 28.8% of high school and middle school e-cigarette users reported using a menthol product.¹² Indeed, as the tobacco industry’s own internal documents demonstrate, the appeal of menthol to youth and other non-tobacco users has been known by the tobacco industry for decades and the role that menthol plays in youth initiation of tobacco products is a core reason for the FDA’s plan to prohibit menthol as a characterizing flavor in combustible cigarettes.

Given the demonstrated appeal of menthol e-cigarettes to youth, FDA’s criteria for evaluating PMTAs for other flavored products must be applied, including the requirement of robust scientific evidence, such as a randomized controlled trial, longitudinal cohort study or similarly compelling evidence demonstrating that the particular menthol-flavored product is not

⁷ *Id.* (emphasis supplied).

⁸ *Id.* at 3, note ii.

⁹ *Id.* at 3.

¹⁰ See Teresa W. Wang et al., *Characteristics of e-Cigarette Use Behaviors Among US Youth, 2020*, 4 JAMA NETWORK OPEN 1, 9 (published online June 7, 2021), <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780705>.

¹¹ *Id.* at 7 tbl.3.

¹² Eunice Park-Lee et al., *E-Cigarette Use Among Middle and High School Students – National Youth Tobacco Survey, United States, 2021*, 70 MORBIDITY & MORTALITY WKLY. REP. 1387, 1388 tbl. (2021), <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7039a4-H.pdf>

only effective in helping smokers stop smoking cigarettes or in significantly reducing the number of cigarettes smoked, but that the menthol product is significantly more effective than tobacco-flavored products and that the difference is large enough to offset the additional risk to youth and other non-tobacco users. While we do not know the content of the pending PMTAs for specific menthol e-cigarettes, the publicly-available studies plainly do not meet the evidentiary standards set by FDA for flavored products.

As a starting point, both the US Surgeon General¹³ and the US Preventive Services Task Force¹⁴ concluded that the evidence that e-cigarettes overall are effective in helping smokers stop smoking cigarettes is “inadequate.” The World Health Organization recently reached a similar conclusion.¹⁵ There is even less evidence for “flavored” e-cigarettes, including menthol e-cigarettes.

The few studies that look at the role of menthol e-cigarettes fall far short of the standard FDA has set. For example, a study conducted by FDA researchers (Rostron et al.) using cross-sectional data found that menthol cigarette smokers who were dual users with e-cigarettes were more likely to use or “preferred” menthol/mint flavored e-cigarettes and less likely to use tobacco-flavored e-cigarettes than non-menthol smoking dual users as were menthol smokers who had switched to e-cigarettes.¹⁶ Thus, 52% of menthol cigarette dual users reported using menthol/mint flavored e-cigarettes, as did 41% of menthol cigarette smokers who had switched compared to 10% and 21.5% respectively for nonmenthol smokers. However, exclusive use of menthol/mint flavored e-cigarettes among menthol smokers was much less common. Exclusive menthol/mint flavor use among menthol smokers was 13% for dual users and 21% for switchers.

At most, the Rostron study shows, unsurprisingly, that menthol cigarette smokers show a preference for menthol and mint e-cigarettes than non-menthol smokers. But this is far from establishing that menthol smokers who switched would not have done so had such e-cigarette flavors not been available. Indeed, in issuing MDOs for other flavored e-cigarette products, FDA has noted the limitations of cross-sectional surveys and studies that assess only consumer preferences,¹⁷ as well as studies, like the Rostron study, that are not product-specific.¹⁸ The

¹³ HHS, Office of the Surgeon General, Smoking Cessation: A Report of the Surgeon General, (2020), <https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf>.

¹⁴ United States Preventive Services Task Force, Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons, Final Recommendation Statement (2021), <https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions>.

¹⁵ World Health Organization, WHO report on the global tobacco epidemic 2021: addressing new and emerging products (2021), <https://www.who.int/teams/health-promotion/tobacco-control/global-tobacco-report-2021>.

¹⁶ Brian L. Rostron et al., *ENDS Flavor Preference by Menthol Cigarette Smoking Status among US Adults, 2018-2019*, 18 INT’L J. ENVTL. RES. & PUB. HEALTH 1 (2021), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7796212/>.

¹⁷ Model TPL at 12.

¹⁸ *Id.* at 11.

Rostron study is not the kind of study FDA has indicated is rigorous enough to demonstrate a benefit to smokers sufficient to outweigh the harm to youth from flavored products.¹⁹

The recent study by Cook et al.²⁰ similarly falls short of satisfying the evidentiary standard FDA has imposed for a showing that a particular flavored product offers a uniquely effective path to smoking cessation. The study found that e-cigarette use was associated with higher odds of smoking cessation among both menthol and non-menthol smokers, but the association was stronger for menthol smokers. However, this analysis was not product-specific and did not consider what flavors were being used and whether *menthol* e-cigarette use was associated with greater likelihood of smoking cessation.

Another recent study authored by researchers associated with Juul Labs²¹ purports to demonstrate that menthol/mint flavored JUULpods yield a unique smoking cessation benefit for menthol smokers, but in fact the study proves nothing of the kind. The study found that adult menthol cigarette smokers were more likely to use menthol/mint flavored JUULpods (53.8%) than non-menthol smokers (22.9%) and that menthol cigarette smokers had higher odds of switching than non-menthol smokers. The authors thus conclude that menthol smokers had higher odds of switching because they had higher rates of using menthol/mint flavored JUULpods, despite clear evidence to the contrary. In fact, *there was no statistically significant difference in switching among menthol smokers who used mint/menthol-flavored JUULpods compared to tobacco-flavored JUULpods.* (To the contrary, the odds of switching were lower for those using mint/menthol-flavored pods, although this was not statistically significant.) In other words, JUULpod flavor was not significantly associated with switching among menthol smokers. This is consistent with another study from Juul Labs finding that no JUULpod flavors, compared to Virginia tobacco-flavored JUUL, were associated with increased rates of switching.²²

Critically important, none of these studies examined the role of menthol e-cigarettes on youth or attracting young adult non-smokers.

¹⁹ FDA also should not rely on studies that assess users' hypothetical responses to menthol cigarette and/or e-cigarette bans, as these findings are poor predictors of actual behavior.

²⁰ Steven Cook et al., *A longitudinal study of menthol cigarette use and smoking cessation among adult smokers in the US: Assessing the roles of racial disparities and E-cigarette use*, 154 PREVENTIVE MED. 1 (2022), <https://www.sciencedirect.com/science/article/pii/S0091743521004552>.

²¹ Nicholas I. Goldenson et al., *Differences in switching away from cigarettes and JUUL use characteristics among adult menthol and nonmenthol smokers who purchased the JUUL System*, 231 DRUG & ALCOHOL DEPENDENCE 1 (2022), <https://www.sciencedirect.com/science/article/pii/S037687162100733X>.

²² Nicholas I. Goldenson et al., *Switching away from Cigarettes across 12 months among Adult Smokers Purchasing the JUUL System*, 45 AM. J. HEALTH BEHAV. 443 (2021), <https://pubmed.ncbi.nlm.nih.gov/33894794/>.

Conclusion

In evaluating PMTAs for flavored e-cigarettes, FDA repeatedly has determined that, given the clear evidence of their harm to youth, no such product can meet the statutory public health standard unless “the strongest types of evidence” are presented that the particular flavored product is more effective than tobacco-flavored products in helping smokers to stop smoking cigarettes or significantly reducing the number of cigarettes smoked and that this benefit is significant enough to outweigh the risk to youth.

Because the risk to youth of menthol-flavored products is real and well-established, no menthol product should receive a marketing order without similarly strong evidence of a countervailing benefit to adult cigarette smokers sufficient to outweigh its harm to youth. The publicly-available studies of menthol-flavored e-cigarettes do not come close to meeting this evidentiary standard. Authorizing a menthol-flavored e-cigarette product without meeting the standard FDA has established for other flavored products would be arbitrary and capricious, and would do great harm to public health. We therefore urge the agency to proceed, without further delay, to deny marketing authorization to all menthol e-cigarettes.

Sincerely,

American Academy of Pediatrics
American Cancer Society Cancer Action Network
American Heart Association
American Lung Association
Campaign for Tobacco-Free Kids
Parents Against Vaping e-cigarettes (PAVe)
Truth Initiative

CC: The Honorable Robert M. Califf, FDA Commissioner