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June 8, 2022

Ms. Michele Mital  
Acting Director, Center for Tobacco Products  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002

RE: FDA's scientific findings in the proposed menthol cigarette rule support denial of menthol-flavored e-cigarette premarket applications

Dear Director Mital:

As you are aware, FDA recently published a proposed rule to prohibit menthol as a characterizing flavor in cigarettes (“proposed rule”).<sup>1</sup> In the Preamble to the proposed rule, FDA presents extensive scientific findings on the pernicious role that menthol plays in increasing initiation of tobacco products,<sup>2</sup> sustaining nicotine dependence, and making it more difficult to stop using tobacco products. FDA’s findings are based on menthol’s flavor and sensory effects as well as evidence that menthol enhances the addictive effects of nicotine, particularly among young people.

FDA examined both the epidemiological evidence and the biological evidence and concluded that both point to the same conclusions that the combination of menthol and nicotine:

- Increases youth initiation;
- Increases youth progression to regular cigarette smoking;
- Increases the intensity of youth addiction; and
- Increases the intensity of adult addiction, making it harder to quit.

Although continued research is needed – the evidence FDA discussed was largely drawn from experience with smokers – there are early scientific indications that these findings apply to

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<sup>1</sup> Tobacco Product Standard for Menthol in Cigarettes, 87 Fed. Reg. 26,454 (proposed May 4, 2022).

<sup>2</sup> In this letter, “tobacco product” refers to products meeting the statutory definition of that term, including synthetic nicotine products. *See* 21 U.S.C. § 321(rr).

other types of tobacco products that combine menthol and nicotine in products inhaled into the lungs, such as e-cigarettes and e-liquids (collectively, “e-cigarettes”). The findings increase the concern that authorization of any menthol-flavored e-cigarette that also delivers nicotine would harm the public health, particularly the health of young people. The scientific findings laid out by FDA in the proposed rule demonstrate that the combination of menthol and nicotine creates risk to youth, and that menthol as a flavoring potentially poses a greater risk to youth than other flavorings because of how it enhances the addictive impact of nicotine-containing products.

The undersigned organizations write to follow up on our [April 5, 2022 letter](#) based on the detailed scientific findings laid out in the proposed rule to urge the FDA to deny, without further delay, marketing authorization to all menthol e-cigarettes.

In the Preamble to the proposed rule, FDA concluded that “menthol in cigarettes increases smoking initiation.”<sup>3</sup> By producing “a minty taste and cooling sensation when inhaled” menthol makes cigarettes more palatable for new users and facilitates “experimentation and regular use, particularly among younger smokers.”<sup>4</sup> These findings directly bear on FDA’s consideration of marketing applications for menthol e-cigarettes because, whether found in cigarettes or e-cigarettes, the flavor and sensory effects produced by menthol make tobacco products easier to inhale and more attractive to new users.

FDA also found that the interaction of menthol and nicotine in the brain enhances nicotine addiction, particularly among young people, resulting in increased nicotine dependence and making it more difficult for users to stop using such products. “[M]enthol, like nicotine, binds to nicotinic receptors in the brain...and menthol alone can increase the number of nicotinic receptors in the brain.”<sup>5</sup> An increase in nicotinic receptors is associated with the development of nicotine addiction.<sup>6</sup> FDA also noted that the combination of these chemicals is particularly damaging to young people: “The combined effects of nicotine and menthol in the developing brain make youth who smoke menthol cigarettes particularly vulnerable to the effects of menthol on nicotine dependence.” The end result is that “menthol facilitates repeated experimentation and progression to regular smoking among youth and young adults.”<sup>7</sup>

FDA presented additional evidence demonstrating that the combined effects of menthol and nicotine also make it more difficult to stop using nicotine-containing products.

When an individual stops smoking, such as overnight or when attempting to quit, the nicotine levels in the brain decrease as the body clears nicotine, but the number of nicotinic receptors does not (Ref. 115). The combination of high levels of nicotinic receptors and low levels of nicotine in the brain produces the discomfort smokers feel when experiencing symptoms of nicotine withdrawal (Ref. 115). This is consistent with reports that smokers with greater brain

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<sup>3</sup> 87 Fed. Reg. 26,463.

<sup>4</sup> *Id.*

<sup>5</sup> *Id.* at 26,457.

<sup>6</sup> *Id.* at 26,468.

<sup>7</sup> *Id.* at 26,465.

nicotinic receptor levels have more difficulty quitting than smokers with lower brain nicotinic receptor levels.<sup>8</sup>

While FDA's discussion related to smokers, its discussion of these findings is based on the relationship between menthol and nicotine in the brain. There is scientific reason to be concerned that they apply to delivery through aerosol as well as through combustion.

Overall, FDA documented the extensive data showing that, "[i]n combination with menthol's flavor and sensory effects, menthol's interaction with nicotine in the brain plays a role in making it easier to experiment, progress to regular smoking and dependence, and harder to quit smoking."<sup>9</sup> These findings rest on menthol's flavor and sensory effects and the interaction between menthol and nicotine in the brain – features that are present in menthol e-cigarettes. Given FDA's own findings that menthol increases initiation of tobacco products, leads to more regular use of tobacco products, makes it harder to stop using such products, makes these products more appealing to youth, and leads to greater youth usage, menthol e-cigarettes cannot meet the public health standard.

This conclusion is not altered by the potential that at some point FDA may prohibit the manufacture, marketing, and sale of menthol cigarettes. As our earlier letter noted, the US Surgeon General, the WHO, and the US Preventive Service Task Force have all concluded that at present the evidence remains "inadequate" to conclude that e-cigarettes are effective at helping smokers stop smoking cigarettes. The evidence is even weaker for menthol e-cigarettes. What is known is that the menthol in inhaled tobacco products poses an enormous risk to youth and that among adults, these products enhance and sustain addiction, unlike FDA-approved cessation products.<sup>10</sup>

Given these findings, we again urge the agency to deny, without further delay, 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, Commissioner of Food and Drugs

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<sup>8</sup> *Id.* at 26,468.

<sup>9</sup> *Id.*

<sup>10</sup> With the risk posed by menthol e-cigarettes, it is noteworthy that no e-cigarette company has applied to the Center for Drug Evaluation and Research to have these products evaluated as cessation products.