February 15, 2019

Mr. Mitchell Zeller
Director, Center for Tobacco Products
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center
Building 71, Room G335
Silver Spring, MD 20993-002

Re: Necessity of adolescent risk perception data in Modified Risk Tobacco Applications

Dear Director Zeller:

We write to express our deep concern that the Food and Drug Administration (FDA) is considering granting Modified Risk Tobacco Product (MRTP) applications without first requiring data concerning how the proposed modified risk claims would affect the risk perception and behavior of adolescents. This issue impacts each pending MRTP application and was the subject of discussion at the February 6-7 TPSAC meeting. What the FDA does with the pending applications will set a precedent for all future applications.

FDA has before it at least four MRTP applications. None have presented data concerning the risk perception of or any meaningful data to project the likely behavioral response of adolescents derived from actually surveying adolescents. At least one of the applications asserts that FDA advised the applicant that provision of such survey data was not required in a modified risk application.[1]

We believe the grant of an MRTP application without the provision of information on the risk perception of adolescents and other meaningful evidence to make a projection of the impact of granting the MRTP application on the likely behavior of adolescents that is derived from surveying adolescents is contrary to statutory requirements, contrary to FDA's own draft guidance, contrary to

[1] Docket No. FDA-2017-D-3001, "Modified Risk Tobacco Product Applications for IQOS system with Marlboro Heatsticks, IQOS system with Marlboro Smooth Menthol Heatsticks, and IQOS system with Marlboro Fresh Menthol Heatsticks submitted by Philip Morris Products, S.A." PMI, Response to November 22, 2017 Information Request, submitted as part of PMI's amended application, at 48-50. (Hereinafter, "PMI").

the conclusions submitted to FDA by the Institute of Medicine, and most important, fundamentally bad policy.

A decision to grant any of these applications or any other MRTP application without requiring data derived directly from adolescents would put our youth at risk in a way the statute was specifically designed to prevent. Adolescents process information, make decisions and respond to stimuli in ways that are different from adults, including young adults. For decades, we have known that virtually all new tobacco users begin as an adolescent or younger, that tobacco industry marketing has been targeted to take advantage of how young people make decisions and perceive risk, and that it is essential to understand how youth perceive different messages and products to understand how they will behave. As the adolescent population consists of both users and non-users of the tobacco products currently available on the market, FDA must consider whether a modified risk claim would reinforce continued use by existing youth users, encourage initiation among non-users or relapse among former users as required by statute.

An application that does not include information obtained directly from youth does not and cannot comply with the Tobacco Control Act. Under §911(g)(1), the burden is on the applicant seeking an order allowing the marketing of the product with a modified risk claim to demonstrate that the product "*as it is actually used by consumers* will (A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." (emphasis added).

Sec. 911(g)(4) further requires FDA to take into account the following specific empirical factors in determining whether the (g)(1) standard has been met:

> (A) The relative health risks to individuals of the tobacco product that is the subject of the application;
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> (B) The increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application;
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> (C) *The increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application*;
>
> (D) The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved under chapter V to treat nicotine dependence.

(emphasis added). Thus, FDA must consider not only the effects of the asserted modified risk product on those who use it, but also its population-wide impact on tobacco use initiation, cessation and relapse Because of the importance of considering likely consumer response to proposed modified risk claims, it is essential for FDA to consider the effect of such claims on the risk perception of consumers. Moreover, given the importance of avoiding youth initiation of tobacco

products as a prime regulatory objective, it is particularly important for FDA to base its decision on accurate data about the impact of proposed modified risk claims on the risk perception of adolescents.

The consequences of not requiring information on the perception and likely behavior of adolescents could not be more serious. FDA is considering these applications at a time when both the Commissioner of the FDA,[2] and the Surgeon General of the United States,[3] have declared that e-cigarette use by the young has reached "epidemic" proportions. Data from the National Youth Tobacco Survey shows that, among high school students, current e-cigarette use increased from 1.5 percent (220,000 students) in 2011, to 20.8 percent (3.05 million students) in 2018. Indeed, e-cigarette use among high school students rose a remarkable 78 percent from 2017-2018. The growing use of e-cigarettes has now reached middle school kids as well, increasing from 0.6 percent in 2011 (60,000 students) to 4.9 percent (570,000 students) in 2018, with a 43 percent increase from 2017-2018 alone.[4] On top of that, recent research has also shown that young people who use e-cigarettes are more likely to become smokers later, and many of these are low-risk youth who would not have otherwise used cigarettes.[5]

There is little doubt that the current epidemic of e-cigarette use among teens is largely the result of the extraordinary appeal to this age group of JUUL, an e-cigarette with a high-tech design that resembles a USB flash drive. In a rare advisory issued in December of last year, U.S. Surgeon General Jerome Adams cited JUUL as "a new type of e-cigarette" that "has become increasingly popular among our nation's youth," citing its 600 percent surge in sales during 2016-2017, giving it the greatest market share of any e-cigarette in the U.S. by the end of 2017, as the epidemic of e-cigarette use among kids began to take hold.

The epidemic caused by JUUL will not be an isolated incident if FDA does not require information about youth perception and behavior. We have already provided FDA with examples of how IQOS is being marketed outside the United States using images and strategies known to impact youth and similar in critical respects to the images and tactics used by JUUL.

The current e-cigarette youth epidemic demonstrates that there is a serious risk that new products, marketed as modified risk products, may attract significant usage among young people, many of whom may never have used a tobacco product. Thus, it is critical that FDA require substantial evidence on the impact of the marketing of such a product as a modified risk product would have on the likelihood of youth initiation of tobacco products before it grants the application.

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[2] Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's continued efforts to address growing epidemic of youth e-cigarette use, including potential new therapies to support cessation (November 2, 2018).
[3] Surgeon General's Advisory on E-Cigarette Use Among Youth (December 18, 2018) (SG Advisory).
[4] Centers for Disease Control and Prevention (CDC), "Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students—United States, 2011-2018," *Morbidity and Mortality Weekly Report (MMWR)*, 67(45):1276-1277, November 16, 2018, https://www.cdc.gov/mmwr/volumes/67/wr/mm6745a5.htm?s_cid=mm6745a5_w. Current use defined as any use in the past month.
[5] Berry, KM, "Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths," *JAMA Network Open* 2(2):e187794. doi:10.1001/jamanetworkopen.2018.7794, 2019.

Modified risk applications that provide no information from surveys that include adolescents cannot meet the statutory standard and should not be granted. No accurate assessment of the impact on the health of the population as a whole can be made without consideration of actual data derived from studies of the perceptions of those under age 18. Indeed, the grant of these applications in the absence of that data would set the worst possible precedent and be wholly inconsistent with FDA's statutory mission to protect the public health.

One applicant has purported to meet the requirement for providing data on youth risk perception by oversampling young adults.[6] However, oversampling of young adults does nothing to inform FDA about the risk perceptions of those in an entirely different age group. Reliance on young adult data as a substitute for evidence about adolescent risk perception will not provide adequate scientific support and, therefore, would be an abuse of discretion.

One of the applications (Philip Morris International or PMI) seeks to explain the absence of adolescent consumer perception data with the conclusory statement that its "internal policy prohibits the conducting of studies relating to tobacco products, which involves under legal age of smoking, a policy that is consistent with recommendations from the FDA."[7] This statement is based on a misreading of FDA's Draft Guidance for the preparation of Modified Risk Tobacco Product Applications.

As that Draft Guidance makes clear, FDA requires only that "all study subjects *receiving tobacco products* are current daily tobacco product users at least 21 years of age"[8] (emphasis added). Not only is this limitation not applicable to studies of promotional material such as modified risk claims to determine the effect of such materials on adolescent risk perception or interest in using the product, but the Draft Guidance makes clear that inclusion of the effect on adolescent perception should be an essential feature of such studies. The Draft Guidance states:

> To address the effect of the MRTP on tobacco use initiation, FDA recommends that applicants submit:
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> - Human studies that evaluate consumer perception of the product, including its labeling, marketing and advertising.
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> These studies should be designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including…:
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> - The likelihood that consumers who have never used tobacco products, *particularly youth and young adults,* will initiate use of the tobacco product;[9] (emphasis added)

Moreover, the Draft Guidance instructs companies to "estimate the attributable risk of all of the various health effects for various types of individuals in the U.S. population, as well as the total

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[6] PMI, Sec. 2.7, p. 126.
[7] *Id.*
[8] Draft Guidance, Modified Risk Tobacco Applications, March 2012, at 29.
[9] *Id*. at 20.

number of individuals of each type." The Draft Guidance goes on to state, "The types of individuals may include, but are not limited to, the following … Non-users who initiate tobacco use with the proposed product, *such as youth*, never users, former users" (emphasis added).[10]

Thus, far from prohibiting the testing of such messages on adolescents, the FDA Draft Guidance characterizes such testing as particularly important. In this light, the failure of these applicants to provide any evidence of the effect of these messages on adolescent risk perception is an inexplicable omission that ignores FDA's specific instruction to include that analysis.

Contrary to PMI's assertion that FDA's policy precludes research regarding consumer perception of youth, FDA's Draft Guidance on MRTP applications describes how such research should be done. Recognizing that research among non-smokers, and non-smoking youth in particular, requires care, FDA offered applicants an opportunity to work with the agency to determine the best way to conduct studies involving youth:

> When designing consumer perception studies, applicants should take care that the studies themselves do not promote use of the product, particularly among vulnerable populations, such as youth, non-users of tobacco products, and pregnant women. FDA recommends that applicants meet with FDA to discuss research plans before embarking on research with vulnerable populations. Section IX.B of this guidance provides information on requesting a meeting with FDA.[11]

The applicants' failure to assess the impact of the marketing of IQOS on youth also contravenes recommendations made by the Institute of Medicine's (IOM) 2012 report, *Scientific Standards for Studies on Modified Risk Tobacco*, which recommended that "FDA should require studies to include populations of special relevance, including (but are not limited to) … adolescents"[12] and included an assessment of the effects on youth as "an essential element in establishing the public health benefit of an MRTP."[13] The report included research on adolescents in three of its "Evidence domains relevant to an MRTP application."[14] The need to consider the effects of promotional statements on youth is vitally important in light of the industry's documented history of marketing tobacco products in ways that attract adolescents and the role that youth initiation has played—and continues to play—in the recruitment of long-term adult smokers.[15]

According to IOM, perceptions of and intentions to use a given MRTP are also likely to differ by age group. Thus, IOM noted that it is "critical that studies include participants in the following age groups: children (≤ 12 years old), adolescents (13–17 years old), young or emerging

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[10] *Id*. at 22.
[11] FDA 2012 Draft Guidance, p. 26.
[12] Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011, at 14 ("IOM report").
[13] IOM report at 50.
[14] IOM report at 7 (Summary).
[15] Report of the Surgeon General (2012), 530-41, 603-27 and sources cited therein; *U.S. v. Philip Morris*, 449 F. Supp. 2d at 561-691.

adults (18–25 years old), adults (≥ 25 years old)."[16] As noted by IOM, "adolescents' perceptions of the risks and benefits of cigarette smoking play an important role in adolescents' decisions to smoke. Given that adolescence is a period of heightened vulnerability for the initiation of tobacco use, it is important to evaluate whether adolescents accurately understand the purported benefits of an MRTP. Of particular importance are adolescents' perceptions of the risks and benefits of using the product, and whether they intend to initiate tobacco use with the MRTP rather than a traditional tobacco product because they believe the former is a "safe" alternative."[17]

It is a spurious argument that research cannot be conducted with youth in an ethical way. The IOM report, like the FDA Draft Guidance, detailed how research on youth perceptions of risk of MRTPs can be conducted consistent with ethical standards of research.[18] For example, IOM suggests that such research could be appropriately done under the supervision of an independent third party.[19] Such a procedure would make it possible for an applicant to develop evidence regarding the effect of the marketing of a product on this population. IOM noted that, "Survey research or perception/messaging research among non-smokers is acceptable where the non-smokers are not being exposed to the product."[20] Furthermore, any information submitted by the applicant must undergo the FDA's rigorous review process and is subject to public comment.

FDA should not grant and should make it clear to manufacturers that no modified risk application will be granted in the absence of survey data evaluating the effect of modified risk claims on risk perception of youth. Granting an application in the absence of such data would contravene the statute and be vulnerable to legal challenge.

Respectfully submitted,

American Academy of Pediatrics

American Cancer Society Cancer Action Network

American Heart Association

American Lung Association

Campaign for Tobacco-Free Kids

Truth Initiative

[16] IOM report at 174.
[17] IOM report at 165.
[18] IOM report at 10.
[19] IOM report at 57.
[20] IOM report at 52.