December 28, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-4188, Draft Guidance for Industry titled "Tobacco Products: Principles for Designing and Conducting Tobacco Product Perception and Intention Studies"

The undersigned public health organizations submit these comments on the above-referenced Draft Guidance which, when finalized, will represent the FDA's current thinking on designing and conducting tobacco product perception and intention (TPPI) studies submitted as part of modified risk tobacco product (MRTP) applications, premarket tobacco product applications (PMTAs), and substantial equivalence reports.

Consistent with the Principles to Guide FDA Premarket Review of E-Cigarettes and Other Deemed Products,[1] which our organizations submitted earlier this year, **the Draft Guidance must be amended to make clear that TPPI studies should provide direct evidence about the potential impacts of the specific product that is the subject of the application on American youth and adolescents (less than 21 years of age) who are currently initiating and using tobacco products in the millions.** An application that does not include information obtained directly from youth and young adults does not and cannot comply with the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act or TCA). Given the unambiguous mandate in the TCA to provide sufficient evidence—on a premarket basis—of the product's population-wide public health impact, it should be clear that such an impact cannot be assessed without direct evidence of a tobacco product's impact to nonusers, especially youth.[2] Indeed, it is remarkable that the Draft Guidance on TPPI studies recommends that applicants "consider the potential impacts to vulnerable populations" yet fails to even mention youth as a "vulnerable population."[3]

A decision to grant any tobacco product marketing order without requiring data in applications 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

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[1] Campaign for Tobacco-Free Kids (CTFK) et al., Principles to Guide FDA Premarket Review of E-Cigarettes and Other Deemed Products, 4 (Aug. 10, 2020), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2020_08_10_Premarket-Principles.pdf.

[2] 21 U.S.C. §§ 387j(a)(3), (c)(4); 21 U.S.C. § 387k(g). *See also* 21 U.S.C. 387 note (2) (stating a purpose of the TCA is "to ensure the [FDA] has the authority to address issues of particular concern to public health officials, *especially the use of tobacco by young people…* ") (emphasis added).

[3] FDA, Tobacco Products: Principles for Designing and Conducting Tobacco Product Perception and Intention Studies: Draft Guidance for Industry, 18 (Oct. 2020), https://www.fda.gov/media/143322/download.

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, as well as potential users of products that could be brought to market, FDA must consider if a modified risk claim or introduction of a new tobacco product would reinforce continued use by existing youth users, encourage initiation among non-users or relapse among former users as required by statute.

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 e-cigarette use by the young has reached "epidemic" proportions and virtually no evidence-based treatment options exist to help nicotine-dependent youth. It is even more critical than ever that the evaluation of new tobacco products and modified risk claims includes rigorous data on the perception and likely behavior of adolescents given this lack of effective treatment options. E-cigarettes are the most commonly used tobacco product among youth, and 3.6 million youth are current e-cigarette users.[4] 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 that attracted youth with flavors and a sleek, high-tech design, while delivering a highly addictive level of nicotine. The epidemic caused by JUUL will not be an isolated incident if FDA does not require information about youth perception and behavior from tobacco manufacturers seeking to market their products or make modified risk claims.

I. It is contrary to the Tobacco Control Act and fundamentally bad policy for FDA to continue to relieve the industry from its obligation to demonstrate in tobacco product applications that their products and claims meet the public health standard.

In March 2012, FDA issued Draft Guidance on MRTP applications that specifically identified youth and young adult tobacco use initiation as a statutorily-mandated "critical population health consideration."[5] The MRTP Draft Guidance makes clear that studies should include the impact of modified risk claims on adolescent risk perceptions and their interest in using the products and that this information is 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.

[4] Teresa W. Wang et al., *E-cigarette Use Among Middle and High School Students – United States, 2020*, 69(37) MORBIDITY & MORTALITY WKLY. REP. 1310 (2020), https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6937e1-H.pdf.

[5] FDA, Modified Risk Tobacco Product Applications: Draft Guidance, 20, 22, 26 (Mar. 2012), https://www.fda.gov/media/83300/download.

> 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;[6] (emphasis added).

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.[7]

FDA also finalized Guidance in June 2019 on PMTAs for e-cigarettes. In it, the agency similarly recognized the need for TPPI studies "among populations of non-users of tobacco products (e.g. vulnerable populations such as youth and young adults)."[8] However, despite these explicit acknowledgments by FDA of the importance of youth and young adult data in tobacco product applications, the proposed PMTA rule issued in September 2019 did not require such evidence. In addition, the agency has issued PMTA marketing orders and MRTP orders for multiple products without sufficient evidence of the products' impact, or potential impact, on American youth.

Public health organizations repeatedly have urged FDA to require applicants for premarket orders and modified risk orders to submit youth perception research related to the specific products and claims that are the subject of the applications.[9] For example, in a February 2019 letter to FDA Center for

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[6] *Id.* at 20.
[7] *Id.* at 26.
[8] FDA, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry, 38 (June 2019), https://www.fda.gov/media/127853/download.
[9] CTFK, Comment Letter on 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., 13-16 (Jan. 3, 2018), https://www.tobaccofreekids.org/assets/images/content/2018_01_03_CTFK_IQOS_comments.pdf; CTFK, Comment Letter on Notice of Meeting re R.J. Reynolds Modified Risk Applications for Camel Snus, 22-24 (Aug. 29, 2018), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/2018_08_29_Camel_snus_TPSAC_comments.pdf; CTFK, Comment Letter on Notice of Meeting re Tobacco Product Application Review, 4-6 (Dec. 7, 2018), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/2018_12_07_CTFK_Comments_premarket_review_meeting.pdf; CTFK et al., Comment Letter on 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, S.A., 2, 8-14 (Feb. 11, 2019), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2019_02_11_Public

Tobacco Products Director Zeller, the undersigned public health organizations expressed great concern that at least four MRTP applications pending before FDA did not include any meaningful data on the impact of the proposed claims on youth behavior. As noted in that 2019 letter, the granting of an MRTP order without any survey data on the risk perceptions of adolescents and other meaningful evidence to determine the impact of the proposed marketing on the likely behavior of adolescents, is contrary to statutory requirements and FDA's own draft guidance, and represents fundamentally bad policy.

The undersigned organizations also jointly issued a set of principles to guide FDA's premarket review of tobacco product applications, which specifically call on the agency to ensure applications include "direct evidence of how American youth (up to age 21) and nicotine-naïve American adults perceive the specific product with its specific components, including its labeling, marketing and advertising, as well as data on use of the specific product by American youth and nicotine-naïve American adults, sufficient to establish that availability of the product will not lead youth and nicotine-naïve adults to initiate, or continue, use of the product or other tobacco products."[10] We further explained the need for this specificity, stating the result of FDA's failure to require such evidence is that products and claims are being authorized even though manufacturers have failed to meet their statutory burden to demonstrate a public health benefit.[11] The importance of such evidence to premarket review, and specific suggestions for protocols

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_Health_Groups_Comments_IQOS_MRPTAs.pdf#asset:492187%3Aurl; CTFK et al., Comment Letter on Modified Risk Tobacco Product Applications for Snus Products Submitted by Swedish Match North America, Inc., 1, 6-11 (May 13, 2019), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/2019_05_13_Comments_Swedish_Match.pdf; CTFK et al., Comment Letter on Modified Risk Tobacco Product Application: Applications for Six Camel Snus Smokeless Tobacco Products Submitted by R.J. Reynolds Tobacco Company, 1-2, 7-13 (May 13, 2019), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/2019_05_13_Comments_Camel_Snus.pdf; CTFK et al., Comment Letter on Proposed Rule for Premarket Tobacco Product Applications and Recordkeeping Requirements, 21-25 (Dec. 16, 2019), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/PublicHealthGroupsCommentsonPMTAProposedRule.pdf; CTFK et al., Comment Letter on Modified Risk Tobacco Product Application: Application for Copenhagen Snuff Fine Cut Submitted by Altria Clients Services LLC on behalf of U.S. Smokeless Tobacco Company LLC, 1-2, 7-13 (Jan. 21, 2020), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/Public-Health-Groups-Comments-on-Modified-Risk-Tobacco-Product-Application-for-Copenhagen-Snuff-Fine-Cut-January-21-2020.pdf#asset:509099%3Aurl; CTFK, Comment Letter on Notice of Meeting re 22nd Century Group Inc.'s Modified Risk Applications for VLN™ King and VLN™ Menthol King, 14-17 (Feb. 7, 2020), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2020_07_07_CTFK_comments_TPSAC_VLN_cigarettes_modified_risk.pdf#asset:509569%3Aurl; CTFK et al., Modified Risk Tobacco Product Applications for VLN™ King and VLN™ Menthol King, Combusted, Filtered Cigarettes, Submitted by 22nd Century Group, 18-19, 20-23 (May 18, 2020), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2020_05_18-Public-Health-Group-Comments.pdf; CTFK et al., Principles to Guide FDA Premarket Review of E-Cigarettes and Other Deemed Products, 3-4 (Aug. 10, 2020), https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2020_08_10_Premarket-Principles.pdf; FDA, February 6, 2019 TPSAC Meeting Transcript, 69-71 (Feb. 6, 2019), https://www.fda.gov/media/122002/download;

[10] *Supra* note 1 at 4.

[11] *Supra* note 1 at 5.

and safeguards to ensure that the research is done with scientific integrity and due protection of study subjects, is presented in the recent commentary by Dr. Halpern-Felsher, et al., in the *Journal of Adolescent Health*,[12] attached to these comments.

The set of principles and Dr. Halpern-Felsher's commentary are consistent with the Institute of Medicine's 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"[13] and included an assessment of the effects on youth as "an essential element in establishing the public health benefit of an MRTP."[14] 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."[15]

The IOM report also detailed how research on youth perceptions of the risks of MRTPs can be conducted consistent with ethical standards of research.[16] For example, IOM suggested that such research could be appropriately done under the supervision of an independent third party.[17] 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."[18]

Members of the Tobacco Products Scientific Advisory Committee (TPSAC), have also raised concerns about the lack of youth data in tobacco product applications. At the February 2019 TPSAC meeting on the MRTP applications for two sets of smokeless products, three different TPSAC participants vocalized such concerns.[19] TPSAC members again expressed considerable apprehension about the continued absence of youth data in the subject applications at the most recent TPSAC meeting earlier this year on the MRTP applications for reduced-nicotine cigarettes. In fact, an additional eight TPSAC participants joined the chorus of three individuals who previously expressed concerns.[20] Dr. Weitzman, referring to

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[12] Bonnie Halpern-Felsher et al., *The Importance of Including Youth Research in Premarket Tobacco Product and Modified Risk Tobacco Product Applications to the Food and Drug Administration*, 67(3) J. ADOLESCENT HEALTH 331 (2020).

[13] Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products* at 14 (December 2011) ("IOM Report").

[14] IOM Report at 50.

[15] IOM Report at 165.

[16] IOM Report at 10.

[17] IOM Report at 57.

[18] IOM Report at 52.

[19] Drs. Weitzman, King, and Bierut commented about the lack of, and challenges with, specific product youth data on a premarket or post-market basis (or both). FDA, February 6, 2019 TPSAC Meeting Transcript, 93-96, 110-13, and 125-26 (Feb. 6, 2019), https://www.fda.gov/media/122002/download.

[20] Drs. Mermelstein, Donny, Hatsukami, Ossip, Thrasher, and Warner as well as Ms. Becenti and Ms. Herndon all commented in one way or another about the absence of youth data. FDA, February 6, 2019 TPSAC Meeting

youth, remarked, "I question the ethics of bringing products forward that don't provide data about the most susceptible group for uptake."[21]

Even CTP's own scientific reviewers have stated concerns that applications have not contained sufficient information to determine the likelihood of product use among never tobacco users, including youth and young adults,[22] or to make inferences about youth and the potential for initiation among young adults.[23] For example, in FDA's Technical Project Lead Review for the marketing orders for Philip Morris' IQOS, FDA's experts on social science issues concluded:

> The social science review concludes that based on the information submitted by the applicant, we have concerns with respect to: the lack of information about youth under age 18, as well as the lack of a discussion of submitted data's applicability to youth and the lack of presentation of the data in stratified categories that would allow us to make inferences about youth, the potential for initiation among young adult never smokers, and the potential for dual use among current smokers with only a one cigarette per day decrease in use frequency. ***Philip Morris Products S.A.'s premarket tobacco product applications do not contain sufficient information to address these concerns from a Social Science perspective***.[24] (emphasis added).

However, this expert observation and conclusion was overruled by the Technical Project Lead of the Office of Science,[25] and the IQOS PMTAs were granted by FDA, based on two studies and limited experience in two different countries (Japan and Italy) with different cultures, different marketing rules and different circumstances. There was no meaningful data or analysis to demonstrate the applicability of the limited experience in those countries to the American setting.

It is also notable that, in July 2020, as part of its exposure modification MRTP orders for IQOS, FDA required Philip Morris to conduct post-market surveillance and studies "designed to monitor individuals under the age of 18" with regard to product awareness and use.[26] In doing so, the agency acknowledged "the uncertainty related to the impact of the modified risk information on youth."[27] Thus, instead of addressing this uncertainty on a premarket basis, as is required by the TCA and urged by essentially all stakeholders other than regulated industry, FDA apparently is content to allow tobacco companies to conduct a natural science experiment on American youth.

The importance of FDA requiring data on the likelihood of increased youth initiation *prior* to issuing marketing orders is underscored by the current crisis of e-cigarette usage among young people, which as

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Transcript, 161-72, 175-84, 288, 295 (Feb. 6, 2019), https://www.fda.gov/media/136252/download. The National Center for Health Research also mentioned the lack of data on youth. *Id.* at 95.

[21] *Id.* at 179.

[22] FDA, PMTA Scientific Review: Technical Project Lead Report for 22nd Century Group, Inc. Products, 63 (Nov. 20, 2019), https://www.fda.gov/media/133633/download.

[23] FDA, PMTA Coversheet: Technical Project Lead Review for PMI Heated Tobacco Products, 83 (April 29, 2019), https://www.fda.gov/media/124247/download.

[24] *Id.*

[25] *Id.*

[26] Letter from FDA to Dr. Jeffrey Walker, CEO, Teton Regulatory Services, on Modified Risk Granted Orders – Exposure Modification, 6 (July 7, 2020), https://www.fda.gov/media/139797/download.

[27] *Id.*

noted previously has been called an epidemic by both the FDA and the U.S. Surgeon General.[28] E-cigarette use among youth has skyrocketed in just a few years and health professionals are struggling with treating more and more youth for nicotine addiction. In the case of e-cigarettes, it is clear that post-market surveillance is too little, too late. Post-market surveillance and studies cannot be considered an adequate substitute for requiring the necessary data as part of the premarket review process for new tobacco products and modified risk claims. Indeed, given that virtually all e-cigarettes for which premarket orders are being sought have been on the market for an extended period of time, there already is extensive post-market data available to inform their applications.

II. The FDA's review of tobacco product applications must require, as a prerequisite for authorization, the submission of direct TPPI evidence specific to American youth.

For tobacco product applications to satisfy the population-wide public health standard set forth by the Tobacco Control Act, FDA must require direct TPPI evidence specific to American youth. As Dr. Halpern-Felsher and colleagues state, "Given that 90% of long-term smokers began smoking as adolescents and the sensitivity of the adolescent brain to nicotine addiction, an assessment of the impact of a tobacco product on youth initiation and progression to established use is essential to any determination of population-wide impact."[29] Further, FDA must also ensure that youth data is collected with the necessary safeguards to protect against the types of industry manipulation of scientific research that led Congress to mandate premarket review in the first place. The failure of the Draft Guidance to articulate what the statute requires of manufacturers' submissions with regard to direct evidence of youth perceptions, and to set out the necessary protocols and safeguards to develop this evidence, is an inexplicable omission that must be remedied.

The policies reflected in the Draft Guidance will play a vital role in shaping the types and quality of evidence submitted as part of tobacco product applications. Additionally, with nearly 50 guidance documents issued by, or including CTP,[30] the importance of guidance documents in communicating FDA policy cannot be overstated. Thus, it is imperative that CTP be as clear as possible about its current thinking on what types of TPPI studies the agency would like to see in tobacco product applications.[31]

Because the applicable premarket authorization statutory standards cannot be met without data specific to American youth, **FDA must amend the Draft Guidance to explicitly state that TPPI data on nonusers specifically includes youth and young adults and should include this statutory requirement**

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[28] FDA, *Think E-Cigs Can't Harm Teens' Health?*, (Apr. 30, 2020), https://www.fda.gov/tobacco-products/public-health-education/think-e-cigs-cant-harm-teens-health; Office of the Surgeon General, HHS, *Surgeon General's Advisory on E-Cigarette Use Among Youth*, (2018), https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf.

[29] *Supra* note 12.

[30] As opposed to only 14 non-duplicative proposed or final rules, *see* FDA, Rules and Regulations, https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/rules-and-regulations (last accessed Dec. 11, 2020). FDA, Search for FDA Guidance Documents, https://www.fda.gov/regulatory-information/search-fda-guidance-documents (last accessed Dec. 11, 2020).

[31] *See, e.g.*, *supra* note 23 (stating the social science review perspective that there is a lack of information about youth under age 18, discussion of the submitted data's applicability to youth, and presentation of data in stratified categories that would allow inferences about both youth and the potential for initiation among young adult never smokers to be made).

in any finalized Guidance. The agency has spelled this out in prior guidance documents,[32] and it should do so in the finalized version of the Draft Guidance as well. Finally, **the Draft Guidance must also be amended to reflect the necessary safeguards applicants should implement to ensure youth and young adults are sufficiently protected during the conduct of TPPI studies and that the data are objective and reliable**. Dr. Halpern-Felsher and colleagues outlined these critical components as well as the types of youth data needed for every tobacco product application.[33] We urge FDA to incorporate these recommendations into the Draft Guidance.

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

[32] *Supra* note 5; *Supra* note 8.
[33] *Supra* note 12.

Journal of Adolescent Health 67 (2020) 331–333

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Commentary

The Importance of Including Youth Research in Premarket Tobacco Product and Modified Risk Tobacco Product Applications to the Food and Drug Administration

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For the past decade, an influx of new tobacco products has entered the U.S. market, including different types of e-cigarettes and heated tobacco products. These products are a source of great concern because youth find them appealing [1,2], harbor misperceptions about them [3,4], and use them to initiate tobacco and nicotine use [2,5,6].

Under the Family Smoking Prevention and Tobacco Control Act of 2009 (TCA) [7], manufacturers must receive authorization from the Food and Drug Administration (FDA) to market a new tobacco product through the Premarket Tobacco Product Application (PMTA) process [7]. It is the manufacturer's burden to show that its product would be "appropriate for the protection of the public health" [7] in its PMTA application to the FDA. In turn, FDA must assess the new product's population-wide impact, accounting for the likelihood that existing users will stop using tobacco products and nonusers will start using them [7].

The TCA mandates similar FDA review and authorization for "modified risk tobacco products" (MRTP), in which a manufacturer seeks to make a claim that the product is less harmful than another tobacco product [7]. Before making such claims, a manufacturer must demonstrate that its product will significantly reduce the risk of tobacco-related disease to users and "benefit the health of the population as a whole," considering both users and nonusers of tobacco products [7].

Given that 90% of long-term smokers began smoking as adolescents [8] and the sensitivity of the adolescent brain to nicotine addiction [6,9], an assessment of the impact of a tobacco product on youth initiation and progression to established use is essential to any determination of population-wide impact for both PMTA and MRTP applications. A comprehensive set of studies should be conducted to determine whether and to what extent product constituents (such as nicotine and flavors) and product marketing and labeling can influence harm perceptions, product appeal, addictive potential, intentions to use, actual use, product switching, and poly use among all youth, including users, nonusers, and potential users. However, FDA's proposed rule on PMTAs, if made final, would not require such evidence [10]. In fact, the FDA has already granted premarket authorization for multiple products (IQOS heated tobacco product, General snus, and Moonlight cigarettes) without sufficient evidence of impact on youth [11–13]. Furthermore, the FDA has not required such evidence for MRTP applications [14]. In July, 2020, FDA authorized the marketing of the IQOS tobacco heating system with a reduced exposure claim without requiring evidence of the claim's impact on youth in the United States [15].

To help ensure that new products will provide a population-wide public health benefit and not lead to more use, for all PMTA and MRTP applications, FDA must require companies to submit premarket data on the potential impact of each new product on youth. Relying on postmarket data is insufficient. Given that the U.S. Surgeon General has concluded that youth usage of e-cigarettes has reached "epidemic proportions" [16], and that thousands of e-cigarette products soon will be subject to FDA review [17], setting and enforcing strict protocols for this process are urgently needed to help ensure the public's health.

Critical Components and Data Needed for Every PMTA and MRTP Application

Based on the literature and an Institute of Medicine report [18], below we list the requirements of youth-focused evidence that should be required in all PMTA and MRTP applications:

Conflicts of interest: The authors have no conflicts of interest to disclose.

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https://doi.org/10.1016/j.jadohealth.2020.06.020

1. Empirical evidence related to harm perceptions, product appeal, and the addictive potential among youth for any proposed tobacco product or claim must be included in every application. Since the TCA places the evidentiary burden on manufacturers, it is likely that some of this research will be funded by the tobacco industry. Given the history of tobacco industry manipulation of research [18], the FDA must establish the following specific safeguards to ensure that the evidence submitted is objective, reliable, and protected from industry influence:
   a. All studies must receive Internal Review Board approval to ensure that the research is ethical and protects human subjects.
   b. All studies should be conducted by a third-party, independent group of investigators. FDA must provide guidelines for study criteria, the research questions to be addressed, the independent groups conducting the research, and the quality checks needed. FDA must also set clear rules on data transparency so that the industry cannot prevent the investigators from presenting the data to the FDA or the public. FDA should also periodically evaluate the independence of the studies and the respective third-party research groups to assess the possibility of industry influence.
   c. All research protocols must be listed on www.clinicaltrials.gov; be accessible to the public; and meet minimum standards for designing, conducting, and reporting results for studies. All study procedures must be stated clearly to be completely transparent and reproducible.
   d. An independent review committee with rotating membership, with no financial ties to the tobacco industry, must be appointed by the FDA to review and approve research protocols. Higher risk protocols should also include an independent Data Safety and Monitoring Board to monitor ongoing progress.
   e. Studies must examine specific risk perceptions related to short- and long-term health outcomes, benefits, risk of addiction, and perceptions of the new product compared with other products already on the market (e.g., including but not limited to cigarettes).
   f. Studies must carefully assess each specific claim, proposed marketing, and promotional efforts, including color and style of the product packaging.
   g. Studies must include examination and documentation of the impact of constituents among youth users. Although such exposure studies are critically important, they need to follow federal and local laws and, as such, may be difficult to conduct among younger youth. In such instances, studies conducted among young adults could be presented, and implications of the findings to younger youth should be discussed.
   h. Studies should include nationally representative youth samples that reflect sufficient sample size with variation in socioeconomic status, race/ethnicity, sex, geographic location, and tobacco use patterns. Findings from different age categories (e.g., adults) should not be inferred to youth, except as discussed earlier.
   i. Proposed studies must follow the guidelines proposed by the National Institute on Drug Abuse for substance use research involving children and adolescents, and if appropriate, for exposure studies in human subjects [19,20].
2. All applications must include a review of existing comparative studies of similar products, including research on adolescent perceptions as they relate to intentions to use and actual use patterns. This review does not replace the requirement of submitting evidence specific to the products and claims being considered.
3. Authorization of any new tobacco product must be based on evidence specific to youth in the U.S. Evidence from other countries can be considered but should not serve as the primary source of information.

As experts on youth tobacco use, we have great concern over the number of new tobacco products entering the U.S. market without authorization and oversight. The FDA must require manufacturers to submit empirical evidence related to the impact on youth for all PMTA and MRTP applications. It is critical that FDA set and enforce strict protocols to ensure scientific integrity and protect youth.

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