Journal of Adolescent Health xxx (2020) 1–3

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

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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