To ensure that its review of new tobacco product applications is not only efficient but also best protects the public health, FDA should communicate and use a process that denies marketing authorization of any new tobacco product has characteristics that appeal to kids, that requires applicants to present data demonstrating impacts of the product on non-users including youth and young adults, that does not allow applicants to use a definition of "switch completely" that includes dual use, and that considers unifying health effects of categories of products

Docket No. FDA–2023–N–2873
Developing FDA's Center for Tobacco Products' Strategic Plan

Lauren Kass Lempert, JD, MPH; Pamela M. Ling, MD, Matthew L. Springer, PhD; Stanton A. Glantz, PhD; Jennifer Fung, PhD; Stuart Gansky, PhD; Wendy Max, PhD; Suzaynn F. Schick, PhD; Minji Kim, PhD*; Bonnie Halpern-Felsher, PhD; Sabrina Islam, PhD; MPH; Vira Pravosud, PhD; Hai-Yen Sung, PhD; Janet Wojcicki, PhD, MPH; Karla Llanes, PhD; Yingning Wang, PhD

UCSF TCORS
*University of South Carolina

August 25, 2023

One of the five proposed goal areas FDA announced it is using to develop a strategic plan for the Center for Tobacco Products (CTP) is: **Ensure Timely, Clear, and Consistent Product Application Review to Protect Public Health.** This goal includes activities related to work processes such as optimizing the efficiency, consistency, and effectiveness of the product application review process; enhancing public understanding of regulatory requirements through transparency and stakeholder engagement efforts; and ensuring that the review process is supported by a strong regulatory science program.[1]

CTP's product application review process is one of the cornerstones of the Family Smoking Prevention and Tobacco Control Act and is central to CTP's mission to use scientific evidence to protect the public health, especially the health of youth, and to advance health equity. In July 2023 FDA reported that it had received applications for more than 26 million new tobacco products and has made determinations on 99% of these applications.[2] This means that 260,000 products are still pending final agency decisions. FDA reported in April 2023 that it had accepted

[1] US Food and Drug Administration, CTP Newsroom, Listening Session: Developing FDA's Center for Tobacco Products' Strategic Plan, August 22, 2023 (July 21, 2023). Available: https://www.fda.gov/tobacco-products/ctp-newsroom/listening-session-developing-fdas-center-tobacco-products-strategic-plan-08222023?utm_campaign=ctp-ruf&utm_content=landingpage&utm_medium=email&utm_source=govdelivery&utm_term=stratcomms#Proposed%20Strategic%20Goals

[2] https://www.fda.gov/tobacco-products/ctp-newsroom/fda-denies-marketing-myblu-menthol-e-cigarette-product

for review applications for 6,698,281 e-cigarette products.[3] However, as of May 2023 FDA had issued Marketing Denial Orders for approximately 6,500 flavored e-cigarette products[4] and as of June 2023, had issued Marketing Granted Orders for 23 tobacco-flavored e-cigarette products and devices,[5] leaving the applications for the products with the largest market shares without final determinations.

For this reason, FDA's goal to optimize the efficiency, as well as the effectiveness, of its new product application process is essential. We suggest some approaches CTP could take that would not only make the process more efficient and effective, but would also better protect the health of youth and other priority populations and be more transparent.

1. **FDA should not authorize the marketing of any new tobacco product that has characteristics that appeal to kids**

- The premarket tobacco product application (PMTA) review process requires FDA to review applications for specific products and to determine whether each specific product is "appropriate for the protection of the public health" (APPH) as statutorily required. When determining whether a product is APPH, the statute requires FDA to weight the likelihood that non-users (including youth) will initiate with the product against the possibility that current users will quit.[6]
- On August 23, 2023, FDA issued warning letters to 15 online retailers for selling and/or distributing unauthorized e-cigarette products packaged to look like youth-appealing characters, school supplies, toys, and drinks. In FDA's announcement, CTP's Director Brian King stated, "The design of these products is a shamelessly egregious attempt to target kids. It's a tough sell that adults using e-cigarettes to transition away from cigarettes need them to look like SpongeBob in order to do so successfully."[7]
- FDA's announcement underscored its understanding that certain product categories such as flavored e-cigarettes that are made to look like candy, drinks, school supplies, or other items that are targeting or especially appealing to youth can never be APPH because the risk these products will be attractive to youth and lead to initiation and addiction outweighs any improbable benefit that their marketing will help current adult users quit.
- FDA must be transparent about its approach and give ample notice of how it intends to analyze PMTA and modified risk tobacco product (MRTP) applications and make marketing authorization decisions. Therefore, FDA should issue a Guidance document that clearly

---

[3] FDA, Tobacco Product Applications: Metrics & Reporting, June 14, 2023. Available: https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-product-applications-metrics-reporting

[4] https://www.fda.gov/tobacco-products/ctp-newsroom/fda-issues-marketing-denial-orders-approximately-6500-flavored-e-cigarette-products

[5] https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders

[6] Family Smoking Prevention and Tobacco Control Act section 910(c)(4), 21 USC section 387j.

[7] FDA, Retailers Warned to Stop Selling Illegal E-cigarettes Resembling Youth-Appealing Characters, School Supplies, Toys, and Drinks, August 23, 2023. Available: https://www.fda.gov/tobacco-products/ctp-newsroom/retailers-warned-stop-selling-illegal-e-cigarettes-resembling-youth-appealing-characters-school?utm_campaign=ctp-enforcement&utm_content=CTPStatement&utm_medium=email&utm_source=govdelivery&utm_term=stratcomms

explains that any new tobacco product seeking marketing authorization that have characteristics that target or are likely to appeal to youth will not receive marketing authorization.

2. FDA should require new tobacco product applications to include data demonstrating impacts of the product on non-users including youth and young adults.

- We submitted a public comment in December 2020 on FDA's draft guidance on Principles for Designing and Conducting Tobacco Product Perception and Intention Studies (TPPI) which we incorporate by reference.[8]
- In that comment, we emphasized that FDA should make clear that it is essential for TPPI studies to specifically evaluate *youth* perceptions and intentions associated with the tobacco products, as well as adult perceptions.
- TPPI studies regarding youth perceptions are particularly important given the fact that 90% of long-term smokers began smoking as adolescents.[9] Moreover, youth are most likely to initiate tobacco use with newer tobacco products such as e-cigarettes. The literature clearly shows that adolescents are the most likely to initiate with and use e-cigarettes. National data from 2019 show that 27.5% of high school students and 10.5% of middle school students reported past 30-day use of e-cigarettes.[10] Among young adults (18-24 years old), 7.6% reported past 30-day e-cigarette use.[11] In contrast, among adults only about 4.2% of those 25-44 and 2.1% of adults 45-64 reported past 30-day e-cigarette use.[12] Youth tobacco use is especially concerning given that the brain continues to develop and change until the mid-20s, making adolescents and young adults especially sensitive to nicotine addiction.[13]

---

[8] Lempert LK, Glantz SA, Ling PM et al. FDA's draft guidance on Principles for Designing and Conducting Tobacco Product Perception and Intention Studies appropriately highlights the importance of determining whether consumers understand the risks of new tobacco products and modified risk claims, but should provide more specific guidelines concerning youth perceptions, measuring intentions to use, addressing perceived benefits, considering effects on bystanders, assessing relapse and dual use, conducting qualitative studies, addressing null findings, and comparing proposed products to products currently commercially available, Docket No: FDA-2019-D-4188, December 21, 2020. Available: https://www.regulations.gov/comment/FDA-2019-D-4188-0015

[9] U.S. Department of Health and Human Services. National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA); 2014

[10] Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. *JAMA*. 2019. doi:10.1001/jama.2019.18387

[11] Villarroel MA, Cha, A.E., Vahratian, A. Electronic Cigarette Use Among U.S. Adults, 2018: NCHS Data Brief No.365. National Center for Health Statistics, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. https://stacks.cdc.gov/view/cdc/87918. Published 2020. Accessed 24 May 2020, 2020.

[12] https://truthinitiative.org/research-resources/emerging-tobacco-products/e-cigarettes-facts- stats-and-regulations

[13] Kim, M., Popova, L., Halpern-Felsher, B., Ling, PM. Effects of e-cigarette advertisements on adolescents' perceptions of cigarettes. Health Communication. 2017 Dec 13:1-8. PMID: 29236550; Kim, M., Ling, PM., Ramamurthi, D., Halpern-Felsher, BL. Youth's perceptions of e-cigarette advertisements with cessation claims. *Tobacco Regulation Science*. 2019 July;5(2):94-104. PMID: 31840040; U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016; Yuan M, Cross SJ, Loughlin SE, et al. Nicotine and the adolescent brain. J Physiol 2015;593:3397-3412.

- It is important, however, that the information to inform this decision making be collected by sources completely independent of tobacco companies and/or tobacco companies' direct or indirect control or financing. Tobacco companies should not conduct studies on youth because of their long history of manipulating research studies including the design, samples and sampling, analyses, and interpretation to be in favor of the industry, and to attract young and new users to their products.[14, 15, 16, 17]
- Therefore, we recommend: (1) all TPPI studies include perception studies on young adults, (2) PMTA and MRTP applications discuss the separate, independent published literature on youth on the same or similar products, and (3) that PMTAs and MRTPs discuss the implications of studies of young adults for predicting youth outcomes.
- A 2012 Institute of Medicine Report[18] and a July 2020 peer-reviewed published commentary[19] on the importance of including youth in studies related to PMTAs, MRTPs, and SEs suggest ways in which the FDA can conduct their own research or fund and oversee external research on the tobacco products submitted through the MRTP or PMTA process to inform its decision making.
- FDA must be transparent about its approach and give ample notice of how it intends to analyze PMTA and MRTP applications and make marketing authorization decisions. Therefore, FDA should make clear that any new tobacco product seeking marketing authorization must **i**nclude data demonstrating impacts of the product on non-users including youth and young adults and must consider *youth and young adult* perceptions associated with tobacco products as well as adult perceptions. However, tobacco companies should not conduct studies on youth directly and should instead follow strict safeguards detailed in our December 2020 comment.

3. In its review of new tobacco product applications, CTP should consider the impact of dual use of the proposed product and not allow applicants to use a definition of "switch completely" that includes dual use.

- In their efforts to demonstrate that products are "appropriate for the protection of the public health," applicants often provide data that they say show that a high percentage of users of the new tobacco product have been shown to "switch completely" from cigarettes to the new product. They claim that the new product is less toxic or harmful than cigarettes, so if users

[14] Bero L. A. (2005). Tobacco industry manipulation of research. *Public Health Reports* (Washington, D.C.: 1974), *120*(2), 200–208. https://doi.org/10.1177/003335490512000215
[15] Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. J Health Polit Policy Law. 1996;21(3):515–42.
[16] Smith, E. A., & McDaniel, P. A. (2016). "The Policy Dystopia Model": Implications for Health Advocates and Democratic Governance. *PLoS medicine*, *13*(9), e1002126. https://doi.org/10.1371/journal.pmed.1002126
[17] *United States v. Philip Morris*, 449 F. Supp. 2d 1 (D.D.C. 2006)
[18] Institute of Medicine 2012. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294. Available: https://www.nap.edu/download/13294
[19] Halpern-Felsher B, Henigan D, Riordan M, Boonn A, Perks SN, Krishnan-Sarin S, Vallone D. The Importance of Including Youth Research in Premarket Tobacco Product and Modified Risk Tobacco Product Applications to the Food and Drug Administration. J Adolesc Health. 2020 Sep;67(3):331-333. doi: 10.1016/j.jadohealth.2020.06.020. Epub 2020 Jul 14. PMID: 32674965

"switch completely" to the new product, the applicant claims the user would have less chance of harmful impacts and/or less exposure to harmful toxicants.

- However, CTP has *de facto* accepted the industry's definition of "switching completely" that allows for substantial dual use (i.e., continued smoking).
- In the case of the MRTP applications for IQOS heated tobacco products (HTP), PM defined "dual use" as "combined use" of IQOS Heatsticks and conventional cigarettes when consumers used 30%-70% Heatsticks out of the total, and PM considered a person who smokes conventional cigarettes up to 30% of the time to have "switched completely" to IQOS. Using this definition, PM presented data claiming that IQOS customers who used IQOS HTPs 70% of the time and smoked cigarettes up to 30% of the time had "switched completely" to IQOS, and therefore IQOS was APPH. Even using their own definition, 22.4% of consumers were dual users.[20]
- Surveys conducted in Korea in 2018 showed that more than 80% of HTP users were using two or more products among HTP, combustible cigarettes, and e-cigarettes.[21]
- However, 30% cigarette use should *not* be considered "switching completely," but rather should be considered "dual use."
- There is a high prevalence of dual use of cigarettes and e-cigarettes among adults, and an increased prevalence of current e-cigarette use among never smokers.[22]
- Among middle and high school students in the US, 3.5% reported current use of multiple (two or more tobacco products) in the 2022 National Youth Tobacco Survey (NYTS).[23]
- Dual use could pose a significant public health risk if it prolongs and sustains nicotine addiction, and consequently inhibits smoking cessation among those who might otherwise quit. Prevalence of current e-cigarette use in smokers with no intention to quit smoking was 18.7% in 2018, and between 2015 and 2018 there was an increase in prevalence (from 3.0% in 2015 to 5.0% in 2018) of current e-cigarette use among never smokers and among former smokers (from 5.3% in 2015 to 12.9% in 2018).[24]
- Dual use of cigarettes along with other products has not been shown to significantly reduce harmful health impacts, and in fact may be more harmful than using cigarettes alone. For example, there may be an increased risk of heart disease for those who use both cigarettes and e-cigarettes.[25]

---

[20] Lempert, Lauren Kass, and Stanton Glantz. "Analysis of FDA's IQOS marketing authorisation and its policy impacts." *Tobacco control* 30.4 (2021): 413-421.

[21] Kim J, Lee S, Kimm H, Lee JA, Lee Cm, et al. (2021) Heated tobacco product use and its relationship to quitting combustible cigarettes in Korean adults. PLOS ONE 16(5): e0251243. https://doi.org/10.1371/journal.pone.0251243

[22] Owusu D, Huang J, Weaver SR, Pechacek TF, Ashley DL, Nayak P, Eriksen MP. Patterns and trends of dual use of e-cigarettes and cigarettes among U.S. adults, 2015-2018. Prev Med Rep. 2019 Oct 25;16:101009. doi: 10.1016/j.pmedr.2019.101009. PMID: 31763161; PMCID: PMC6861646.

[23] Park-Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco Product Use Among Middle and High School Students — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1429–1435. DOI: http://dx.doi.org/10.15585/mmwr.mm7145a1

[24] Owusu D, Huang J, Weaver SR, Pechacek TF, Ashley DL, Nayak P, Eriksen MP. Patterns and trends of dual use of e-cigarettes and cigarettes among U.S. adults, 2015-2018. Prev Med Rep. 2019 Oct 25;16:101009. doi: 10.1016/j.pmedr.2019.101009. PMID: 31763161; PMCID: PMC6861646.

[25] Alzahrani T., Pena I., Temesgen N., Glantz S.A. Association between electronic cigarette use and myocardial infarction. *Am. J. Prev. Med.* 2018;55(4):455–461.

- Consistent with a nonlinear dose-response, a meta-analysis of the effects of reducing cigarette consumption conducted by FDA[26] found no all-cause mortality benefit. Another study[27] found smoking just one cigarette a day generates about 53% of the risk of coronary heart disease for men and 38% for women, and generates 64% risk of stroke for men and 36% for women as smoking 20 cigarettes a day.
- CTP should consider the likelihood that users of a new tobacco product that is the subject of a PMTA and/or MRTP applications will be dual users, and therefore should take into account the concomitant health impacts of dual use of the proposed new product with other tobacco products and/or cannabis when determining whether a proposed new tobacco product is appropriate for the protection of the public health.
- CTP should be transparent about how it will review and analyze new tobacco product PMTA and MRTP applications. It should issue a Guidance document stating that dual product use will be an important factor in its analysis of whether a new tobacco product is appropriate for the protection of the public health and that it defines "switching completely" as switching *completely*, i.e., stopping all cigarette consumption. In particular, FDA should not accept the industry's definition that defines using cigarettes 30% of the time while also using other tobacco products as "switching completely."

4. To expedite product application review, CTP should consider the unifying health effects of categories of products in determining whether a specific product that is the subject of a particular new tobacco product application is appropriate for the protection of the public health.

- CTP should consider that recent studies show that some cardiovascular disease impacts are similar for several inhaled tobacco products including cigarettes, e-cigarettes, heated tobacco products (HTPs), and cannabis. These studies indicate the value of assessing downstream health effects of a new product based on functional testing even if a specific subset of known harmful chemicals is not present.
- Examples of what has been reported for humans and rodents are as follows:

[26] Chang JT, Anic GM, Rostron BL, Tanwar M, Chang CM. Cigarette Smoking Reduction and Health Risks: A Systematic Review and Meta-analysis. *Nicotine Tob Res.* 2021;23(4):635-642.
[27] Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ.* 2018;360:j5855.

    - Endothelial function in rats is comparably impaired by cigarettes, HTPs, or e-cigarettes; no one ingredient is responsible[28, 29, 30, 31, 32, 33, 34]
    - Repeated use of these products increases blood pressure and platelet aggregation, and exerts multiple adverse cardiac effects in rats[35, 36]
    - Endothelial function is comparably impaired by chronic smoking and chronic e-cigarettes use in humans[37]
    - Chronic smoking and e-cigarette use each result in serum that impairs NO release from cultured endothelial cells[37]
    - Chronic smoking and chronic e-cigarette use induce expression of distinct subsets of proteins involved in inflammation, oxidative stress, and thrombosis[37]
- CTP should be transparent and explain in a Guidance that when it is reviewing new tobacco product applications, it will prioritize data demonstrating these unifying functional effects over data on exposure to specific individual chemicals or toxicants. A product that has lower exposure to a number of toxicants but still impairs endovascular function similar to cigarettes would not be appropriate to market as "modified risk".

[28] Pinnamaneni K, Sievers RE, Sharma R, Selchau AM, Gutierrez G, Nordsieck EJ, Su R, An S, Chen Q, Wang X, Derakhshandeh R, Aschbacher K, Heiss C, Glantz SA, Schick SF, Springer ML. Brief exposure to secondhand smoke reversibly impairs endothelial vasodilatory function. *Nicotine Tob Res* 2014;16(5):584-90 (PMC3977486)
[29] Wang, Xiaoyin, et al. "One minute of marijuana secondhand smoke exposure substantially impairs vascular endothelial function." *Journal of the American Heart Association* 5.8 (2016): e003858.
[30] Liu J, Wang X, Narayan S, Glantz SA, Schick SF, Springer ML. Impairment of endothelial function by little cigar secondhand smoke. *Tob Regul Sci* 2016;2(1):56-63 (PMC4703945)
[31] Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob P, 3rd, Springer ML. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tob Control* 2018;27:s13-s9 (PMC6202192)
[32] Rao P, Liu J, Springer ML. JUUL and combusted cigarettes comparably impair endothelial function. *Tob Regul Sci* 2020;6(1):30-7 (PMC6953758)
[33] Rao P, Han DD, Tan K, Mohammadi L, Derakhshandeh R, Navabzadeh M, Goyal N, Springer ML. Comparable Impairment of Vascular Endothelial Function by a Wide Range of Electronic Nicotine Delivery Devices. *Nicotine Tob Res* 2022;24:1055–62 (PMC9199952)
[34] Nabavizadeh P, Liu J, Rao P, Ibrahim S, Han DD, Derakhshandeh R, Qiu H, Wang X, Glantz SA, Schick SF, Springer ML. Impairment of Endothelial Function by Cigarette Smoke Is Not Caused by a Specific Smoke Constituent, but by Vagal Input From the Airway. *Arterioscler Thromb Vasc Biol* 2022;42(11):1324-32 (PMC9616206)
[35] Wang X, Qiu H, Han DD, Tan K, Derakhshandeh R, Springer ML. Abstract 9869: Adverse Effects of Smoking/Vaping of Several Types of Tobacco Products and Marijuana on Cardiac Function and Platelet Aggregation. *Circulation* 2021;144(Suppl_1):A9869-A
[36] Qiu H, Zhang H, Han DD, Derakhshandeh R, Wang X, Goyal N, Navabzadeh M, Rao P, Wilson EE, Mohammadi L, Olgin JE, Springer ML. Increased vulnerability to atrial and ventricular arrhythmias caused by different types of inhaled tobacco or marijuana products. *Heart Rhythm* 2023;20(1):76-86 (PMC10006068)
[37] Mohammadi L, Han DD, Xu F, Huang A, Derakhshandeh R, Rao P, Whitlatch A, Cheng J, Keith RJ, Hamburg NM, Ganz P, Hellman J, Schick SF, Springer ML. Chronic E-Cigarette Use Impairs Endothelial Function on the Physiological and Cellular Levels. *Arterioscler Thromb Vasc Biol* 2022;42(11):1333-50