FDA should prioritize direct measures of health and behavioral effects over indirect measures or assumptions in making regulatory decisions

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Developing FDA's Center for Tobacco Products' Strategic Plan

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FDA announced[1] a Public Meeting and Listening Session and an opportunity to submit written public comments to obtain feedback on five proposed goals it is using to develop a strategic plan for FDA's Center for Tobacco Products' (CTP) comprehensive Strategic Plan. In particular, CTP asked, "What are three specific actions CTP could take in the next 5 years that would have the most impact in significantly reducing tobacco-related death and disease?" ***One of these three specific actions should be to establish a policy of prioritizing direct measures of health and behavioral effects over indirect measures or assumptions whenever possible when making regulatory decisions.***

This principle particularly applies to the following strategic goals 1, 2, and 4:

1. Develop, Advance, and Communicate Comprehensive and Impactful Tobacco Regulations and Guidance.

2. Ensure Timely, Clear, and Consistent Product Application Review to Protect Public Health.

4. Improve Public Health by Enhancing Knowledge and Understanding of CTP Tobacco Product Regulation and the Risks Associated with Tobacco Product Use.

Since at least 1972, tobacco companies have promoted four premises: (1) reduced toxicity indicates reduced risk; (2) collaboration with the tobacco industry will not undermine tobacco control; (3) nicotine addiction is unavoidable; (4) to curtail cigarette use, solutions must be consumer-approved (i.e., profitable), as exemplified in efforts to influence the British

[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

Independent Scientific Committee on Smoking and Health.[2] Companies often worked through scientists with undisclosed connections to industry to promote the industry view of harm reduction, as exemplified in an unsigned editorial in *The Lancet* authored by Michael Russell endorsing RJ Reynolds' Premier heated tobacco product for harm reduction.[3] Tobacco companies also had some success in lobbying the Institute of Medicine to recommend a tiered claims system (with separate tiers for exposure and risk, which they believed would ease the process of qualifying for a claim) in its 2001 FDA-commissioned report *Clearing the Smoke,*[4] which, in turn, influenced the 2009 Family Smoking Prevention and Tobacco Control Act.[5]

The essential argument for focusing on biomarkers was that because new products would not have been in widespread use long enough for health effects to be manifest at the individual or population levels, assessment of these products would have to be limited to biomarker analysis and short-term toxicology studies rather than human evidence. FDA has *de facto* adopted this position in its marketing authorizations for Philip Morris' IQOS[6] heated tobacco product and RJ Reynolds' Vuse Solo[7] e-cigarette.

The theoretical problem that real-world human evidence is not available does not apply to e-cigarettes. Because of the combined effect of the delay in FDA issuing the Deeming Rule taking authority over e-cigarettes until 2016, FDA's enforcement discretion decision to delay the requirement for e-cigarettes to submit premarket applications, and FDA allowing e-cigarettes to remain on the market while it processed PMTAs, e-cigarettes have been on the market and used by consumers for 17 years (since 2006).

Even following Philip Morris' recommendation to the Institute of Medicine *Clearing the Smoke* committee to wait 5 years before starting to consider epidemiology studies,[8] this is more than enough time to obtain and consider epidemiological evidence.

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[2] Elias J, Ling PM. Origins of tobacco harm reduction in the UK: the 'Product Modification Programme' (1972-1991). Tob Control. 2018 Jul;27(e1):e12-e18. doi: 10.1136/tobaccocontrol-2017-054021. Epub 2018 Jan 12. PMID: 29330172; PMCID: PMC6089384.

[3] Elias J, Ling PM. Invisible smoke: third-party endorsement and the resurrection of heat-not-burn tobacco products. Tob Control. 2018 Nov;27(Suppl 1):s96-s101. doi: 10.1136/tobaccocontrol-2018-054433. Epub 2018 Jun 6. PMID: 29875153; PMCID: PMC6238082.

[4] Stratton K, Shetty P, Wallace R, Bondurant S (2001) Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington, D.C.: National Academy Press.

[5] Tan CE, Kyriss T, Glantz SA. Tobacco company efforts to influence the Food and Drug Administration-commissioned Institute of Medicine report Clearing the Smoke: an analysis of documents released through litigation. PLoS Med. 2013;10(5):e1001450. doi: 10.1371/journal.pmed.1001450. Epub 2013 May 28. PMID: 23723740; PMCID: PMC3665841.

[6] Lempert LK, Glantz S. Analysis of FDA's IQOS marketing authorisation and its policy impacts. Tob Control. 2020 Jun 29:tobaccocontrol-2019-055585. doi: 10.1136/tobaccocontrol-2019-055585. Epub ahead of print. PMID: 32601147; PMCID: PMC7952009.

Lempert LK, Bialous S, Glantz S. FDA's reduced exposure marketing order for IQOS: why it is not a reliable global model. Tob Control. 2022 Aug;31(e1):e83-e87. doi: 10.1136/tobaccocontrol-2020-056316. Epub 2021 Apr 2. PMID: 33811155; PMCID: PMC8486889.

[7] Glantz S, Lempert LK. Vuse Solo e-cigarettes do not provide net benefits to public health: a scientific analysis of FDA's marketing authorisation. Tob Control. 2023 Feb 9:tobaccocontrol-2022-057296. doi: 10.1136/tc-2022-057296. Epub ahead of print. PMID: 36764683; PMCID: PMC10409877.

[8] Philip Morris. Fig 1-Reduced_Risk Product Usage 41.Ppt. 20 Jan 2004. http://legacy.library.ucsf.edu/tid/zie30i00.

Moving beyond a focus on biomarkers is particularly important because e-cigarette aerosol contains thousands of chemicals,[9] which may pose *different, even new,* risks than cigarettes. By limiting discussion to a few toxicants (generally based on combusted cigarette smoke), FDA could be missing important health effects. In addition, directly observed disease patterns in people are a more direct assessment of health and behavioral effects of e-cigarettes than biomarkers.

As summarized in a public comment submitted regarding FDA's proposed menthol product standard for cigarettes,[10] there is a large epidemiological literature on health effects of e-cigarettes as actually used in the general population. This literature shows elevated risks for cardiovascular, pulmonary, and oral diseases. In contrast to studies focusing on biomarkers, the direct human epidemiology shows that risks for e-cigarettes for cardiovascular and oral diseases are similar to cigarettes and while lower than smoking for pulmonary disease, e-cigarette risks are much larger than FDA has assumed. Dual use or use of both cigarettes and e-cigarettes (versus exclusive use of either product) is associated with increased odds of disease across all outcomes that were examined.

Likewise, there is a large literature on effects of e-cigarette use on smoking behavior in both youth and adults that is inconsistent with the FDA's assumption that e-cigarettes promote "switching completely" in a way that would reduce harm.

There is also a large epidemiological literature on the relationship between e-cigarette use and cigarette smoking behavior that shows that, as consumer products, e-cigarette use is not

[9] Tehrani MW, Newmeyer MN, Rule AM, Prasse C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography-High-Resolution Mass Spectrometry. Chem Res Toxicol. 2021 Oct 5. doi: 10.1021/acs.chemrestox.1c00253. Epub ahead of print. PMID: 34610237.

[10] Glantz SA; Nhung Nguyen, PhD; Lempert LK; Mohammadi L; Sung H-Y; Matthay M; Da Silva ALO; Cheng J; Gaiha S; Guerra C; Halpern-Felsher B; Max W; Schaffer C; Wang Y; Ling PM (UCSF TCORS). Actual human disease data contradicts the low assumed e-cigarette risk FDA uses to justify an exception for "reduced risk" cigarettes in its product standard prohibiting menthol. Docket No. FDA-2021-N-1349 for "Tobacco Product Standard for Menthol in Cigarettes." August 1, 2022. https://www.regulations.gov/comment/FDA-2021-N-1349-175350

associated with smoking cessation[11, 12, 13, 14] and that youth who initiate nicotine use with e-cigarettes have increased odds of smoking cigarettes.[15]

To implement the ***policy of prioritizing direct measures of health and behavioral effects over indirect measures or assumptions whenever possible when making regulatory and other decisions***:

- FDA should make decisions about risks of e-cigarettes and other established products based on documented effects on disease in the population, not just short-term measures of a limited number of cigarette-based biomarkers.

- FDA should heed its own meta-analysis[16] and stop assuming that reducing, but not stopping, cigarette smoking substantially reduces risks until such time as it presents strong population-based evidence to the contrary.

- FDA should prioritize the effects of dual and poly product use in regulatory and public communication decision making.

- FDA should complete and publish its own assessment of the epidemiological evidence of disease risk associated with e-cigarette use compared to cigarette use and dual use in the general population.

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[11] Wang RJ, Bhadriraju S, Glantz SA. E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis. Am J Public Health. 2021 Feb;111(2):230-246. doi: 10.2105/AJPH.2020.305999. Epub 2020 Dec 22. PMID: 33351653; PMCID: PMC7811087.
Hedman L, Galanti MR, Ryk L, Gilljam H, Adermark L. Electronic cigarette use and smoking cessation in cohort studies and randomized trials: A systematic review and meta-analysis. Tob Prev Cessat. 2021 Oct 13;7:62. doi: 10.18332/tpc/142320. PMID: 34712864; PMCID: PMC8508281.

[12] Nguyen N, Koester KA, Kim M, Watkins SL, Ling PM. "I'm both smoking and vaping": a longitudinal qualitative study of US young adults who tried to quit smoking cigarettes by using electronic cigarettes. Tob Control. 2023 Apr 18:tc-2022-057804. doi: 10.1136/tc-2022-057804. Epub ahead of print. PMID: 37072166.

[13] Osibogun O, Bursac Z, Maziak W. Longitudinal transition outcomes among adult dual users of e-cigarettes and cigarettes with the intention to quit in the United States: PATH Study (2013-2018). Prev Med Rep. 2022 Feb 28;26:101750. doi: 10.1016/j.pmedr.2022.101750. PMID: 35256929; PMCID: PMC8897625.

[14] Chen R, Pierce JP, Leas EC, Benmarhnia T, Strong DR, White MM, Stone M, Trinidad DR, McMenamin SB, Messer K. Effectiveness of e-cigarettes as aids for smoking cessation: evidence from the PATH Study cohort, 2017-2019. Tob Control. 2023 Aug;32(e2):e145-e152. doi: 10.1136/tobaccocontrol-2021-056901. Epub 2022 Feb 7. PMID: 35131948; PMCID: PMC10423520.

[15] Khouja JN, Suddell SF, Peters SE, Taylor AE, Munafò MR. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. Tob Control. 2020 Mar 10;30(1):8–15. doi: 10.1136/tobaccocontrol-2019-055433. Epub ahead of print. PMID: 32156694; PMCID: PMC7803902.
Yoong SL, Hall A, Turon H, Stockings E, Leonard A, Grady A, Tzelepis F, Wiggers J, Gouda H, Fayokun R, Commar A, Prasad VM, Wolfenden L. Association between electronic nicotine delivery systems and electronic non-nicotine delivery systems with initiation of tobacco use in individuals aged < 20 years. A systematic review and meta-analysis. PLoS One. 2021 Sep 8;16(9):e0256044. doi: 10.1371/journal.pone.0256044. PMID: 34495974; PMCID: PMC8425526.

[16] 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.

- FDA should stop making regulatory and public communication decisions on the assumption that e-cigarettes as consumer products help people stop smoking until there is strong population-based evidence that this assumption is correct.

- FDA should complete and publish its own assessment of the relationship between e-cigarette and other tobacco use among youth and young adults, particularly the extent to which e-cigarettes are attracting youth at low risk of nicotine initiation with cigarettes and the extent to which youth who initiate nicotine use with e-cigarettes move to or add cigarettes or other tobacco products.

The FDA should also prioritize direct human evidence when assessing the risks of other new products to the extent possible.