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December 21, 2021

Dr. Janet Woodcock, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD. 20993

By Email: janet.woodcock@fda.hhs.gov

RE: Immediate Need for FDA to Reconsider its October 12, 2021 Marketing Granted Orders for Vuse Solo E-cigarettes

Dear Dr. Woodcock:

On October 12, 2021, FDA authorized the marketing[1] of RJ Reynolds Vuse Solo e-cigarette products through the Premarket Tobacco Product Application (PMTA) pathway. Although in the press release[2] announcing its decision, FDA Center for Tobacco Products Director Mitch Zeller said that the authorizations demonstrated "FDA's robust, scientific premarket evaluation," our review of the FDA's Technical Project Lead[3] (TPL) summary of its scientific justification revealed that the applicant did not prove (as required by law[4]) that the continued marketing of these products is "appropriate for the protection of the public health." In addition, FDA's scientific justification failed to include important studies and much of the broad scientific literature on e-cigarettes.

As we describe in detail below, FDA made several favorable assumptions on RJR's behalf that are not supported by the evidence presented or the scientific literature. FDA is

[1] FDA, Premarket Tobacco Product Marketing Granted Orders. R.J. Reynolds Vapor Company, Vuse Solo Power Unit, Vuse Replacement Cartridge Original 4.8% G1, Vuse Replacement Cartridge Original 4.8% G2, PM0000551, PM0000553, PM0000560. Available: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders

[2] FDA News Release, FDA Permits Marketing of E-cigarette Products, Marking First Authorization of its Kind by the Agency. October 12, 2021. Available: https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-e-cigarette-products-marking-first-authorization-its-kind-agency

[3] FDA, Technical Project Lead (TPL) Review of PMTAs, Submission tracking numbers PM0000551, PM0000553, PM0000560. Available: https://www.fda.gov/media/153017/download

[4] Family Smoking Prevention and Tobacco Control Law section 910(c)(4), Pub L 111-31, June 22, 2009.

currently in the process of reviewing thousands of PMTAs for other e-cigarette products, and its unsupportable authorization of Vuse Solo must not be used as a template for authorizing the marketing of Juul or any other non-flavored (except menthol) closed system e-cigarette. Further, on the basis of the scientific evidence and the best current scientific literature that we describe below, we urge FDA to withdraw its marketing granted orders for Vuse Solo because FDA is r*equired*[5] to withdraw a marketing granted order if it finds that the marketing of the product is not appropriate for the protection of the public health. Careful consideration of the complete scientific literature supports withdrawal of the order.

Summary of scientific issues with Vuse Solo marketing order

FDA failed to present direct quantitative evidence that authorizing the sale of Vuse Solo would have a net positive effect on public health. In a press release on August 26, 2021, Director Zeller explicitly described the trade-off between costs to youth and potential benefits to adults of e-cigarettes: "Companies who want to continue to market their flavored ENDS [electronic nicotine delivery systems, in this context, e-cigarettes] products must have robust and reliable evidence showing that their products' potential benefit for adult smokers outweighs the significant known risk to youth."[6] Understanding the common meaning of the term "outweigh" – "to exceed in weight, value, or importance"[7] – Director Zeller clearly recognized that the determination is an explicitly quantitative comparison.

Most important, while FDA is willing to trade off addicting new youth to Vuse to help current cigarette smokers by implicitly concluding that "potential benefit for adult smokers outweighs the significant known risk to youth,"[8] FDA has the benefit of the fact that e-cigarettes have been sold in the United States for 15 years, so their impact on adult smokers and youth has been quantified. This is very different from a premarket prediction about the impact of a product on public health that has not been actually available in the United States. Nevertheless, ***FDA never explicitly states how many youth the FDA is willing to sacrifice, nor discusses the immediate adverse health effects on these youth, nor states the number of adult smokers who will benefit and by how much. This human accounting must be explicitly included because it is central to the tradeoff FDA has made.***

This failure to quantify the benefits vs. the risks is a fatal flaw in the marketing order because it makes it impossible for FDA to substantiate its determination that authorizing the marketing of Vuse Solo will actually provide a net improvement to public health.

In addition to highlighting FDA's fundamental flaw of not providing a quantitative analysis, this letter presents scientific evidence supporting the points listed below that show that the continued marketing of these products is *not* appropriate for the protection of the public health, and therefore FDA must withdraw its marketing granted orders for Vuse Solo products:

[5] Family Smoking Prevention and Tobacco Control Law section 910(d), Pub L 111-31, June 22, 2009.
[6] FDA News Release, FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health August 26, 2021. Available: https://content.govdelivery.com/accounts/USFDA/bulletins/2ee8e79
[7] Merriam-Webster dictionary. Available: https://www.merriam-webster.com/dictionary/outweigh
[8] FDA News Release, FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health August 26, 2021. Available: https://content.govdelivery.com/accounts/USFDA/bulletins/2ee8e79

- FDA did not adequately consider Vuse's popularity with kids and unacceptably trades off youth addiction for unproven adult benefit.
- FDA misstates the evidence showing that youth e-cigarette use stimulates cigarette smoking, including making the false statement, "Overall, the available evidence to date does not adequately address whether new product use in youth and young adults leads to regular smoking," which ignores more than 17 scientific studies.
- FDA failed to address the evidence that huge numbers of kids are being recruited to nicotine addiction through e-cigarettes.
- FDA places heavy weight on the *assumption* that prohibiting flavors (other than menthol) will deter kids from using Vuse.
- FDA ignored the consistent evidence that e-cigarettes in use as consumer products do not help smokers quit and that they promote relapse in former smokers.
- FDA did not address the finding that about a quarter of adult non-tobacco users could be interested in using the product despite the fact that there is no public health benefit of recreational e-cigarette use or for non-tobacco users.
- FDA ignored the evidence that dual use (when smokers add e-cigs rather than "switching completely") is more dangerous than smoking.
- FDA's discussion of health effects was shallow, focusing on the fact that e-cigs deliver lower levels of *some* toxins while ignoring or downplaying the large body of evidence of substantial specific harms.
- The FDA mentions but does not act on its own study showing no all-cause mortality benefit of smoking reduction.
- FDA considers e-cigarettes having high addictive potential to be a good thing; high abuse liability can enhance youth addiction and can undermine tobacco cessation.

Just two facts make it highly unlikely that *any* e-cigarette can demonstrate a net public health benefit, which is necessary to meet the legal standard of being "appropriate for the protection of public health:" (1) millions of youth are attracted to e-cigarettes, and (2) there is no population benefit on smoking cessation of e-cigarettes when used as consumer products. Without cessation benefit (what the FDA and the tobacco companies call "switching completely) there is no benefit to trade off against the millions of kids being seeing recruited to nicotine addiction.

This means that to obtain a marketing order for a particular e-cigarette, in this case Vuse Solo, the applicant would have to present evidence that the specific features of the product in question make it behave substantially differently than e-cigarettes in general.

In contrast, a careful read of FDA's Technical Project Lead report[9](TPL) reveals that it is filled with incomplete and contradictory information that consistently gives RJR the benefit of

[9] Berran Yucesoy, Deputy Director, CTP Division of Nonclinical Science, with concurrence by Matthew R. Holman, Director, CTP Office of Science. Technical Project Lead {TPL} Review of PMTAs PM0000SSl,

the doubt. However, the law places the burden on RJR, the applicant, to demonstrate that its product is appropriate for the protection of the public health.

FDA's pattern of making favorable assumptions on RJR's behalf sets a dangerous precedent for other e-cigarettes. FDA's TPL for Vuse provides a template for authorizing marketing for Juul or any other non-flavored (except menthol) closed system e-cigarette.

For these reasons, FDA should reassess Vuse Solo in light of the full scientific literature and withdraw its unsupported marketing order.

Failing that, FDA should take the problems identified in this letter[10] seriously and be more rigorous in assessing the remaining PMTA applications for e-cigarettes. As noted above, absent specific reliable quantitative evidence that shows that a proposed product will have very different effects on youth use and adult quitting behavior than e-cigarettes in general, FDA should deny the remaining PMTAs.

FDA did not adequately consider the Vuse brand's popularity with kids and unacceptably trades off youth addiction for unproven adult benefit

As a starting point, in determining whether to grant a marketing order for a new tobacco product for which a PMTA has been submitted, FDA must meet the statutory public health standard laid out in section 910(c) of the Family Smoking Protection and Tobacco Control Act. This law requires FDA to deny an application if the applicant fails to demonstrate that permitting the marketing of the product would be "appropriate for the protection of the public health" and requires FDA to assess "the risks and benefits of the population as a whole, including users and nonusers of the tobacco product." This population-wide assessment must take into account, (A) "the increased or decreased likelihood that existing users of tobacco products will stop using such products," and (B) "the increased or decreased likelihood that those who do not use tobacco products will start using such products."[11] To meet this burden, FDA has stated that the applicant must show that the marketing of the product will yield actual benefits to public health, and the PMTA must contain "sufficient valid scientific evidence to demonstrate that the potential risks and benefits of the marketing of the new tobacco product would have a net positive effect on the health of the population as a whole…"[12]

This point was amplified several times in the Surgeon General's 2020 Report[13] which stated, "the potential benefit of e-cigarettes for cessation among adult smokers cannot come at the expense of escalating rates of use of these products by youth" (p. 25). The Report elaborated this statement: "at the population level, any potential benefits these products confer in terms of

PM0000553, PM0000560. October 12, 2021. Available: https://www.fda.gov/media/153017/download. (cited as TPL below)

[10] This letter addresses the scientific problems with the Vuse Solo marketing order; it does not address problems with the weak marketing restrictions.

[11] Family Smoking Protection and Tobacco Control Act section 910(c)(4), Pub L 111-31, June 22, 2009.

[12] Food and Drug Administration, Premarket Tobacco Product Applications and Recordkeeping Requirements, Proposed Rule, 09/25/2019. 84 FR 50566, 50618.

[13] U.S. Department of Health and Human Services. *Smoking Cessation. 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, 2020.

increasing cessation among adult smokers would need to outweigh potential risks related to use among youth [citing 2014 Surgeon General's Report] including the already unprecedented increase in the use of e-cigarettes among youth that has occurred in recent years [citations omitted] (p. 532), and "… at the population level, any potential benefits [e-cigarettes] confer in terms of increasing cessation among adult smokers would need to outweigh potential risks related to increased initiation of tobacco product use among youth…. When considering public health, in order for a net gain to occur, any benefit of e-cigarette use among adult smokers would have to outweigh the risks of increased initiation among young people at the population level." (p. 652-653)

Despite the statutory mandate, FDA's own interpretation of that mandate, and the conclusions of the Surgeon General, in granting the marketing orders for Vuse Solo, FDA failed to appropriately weigh the significant and documented risks of increased initiation and youth addiction against the largely unsubstantiated benefits to adult smokers.

Further, despite the importance of youth use, FDA did not require specific direct evidence on youth use of Vuse Solo or on the susceptibility of youth to it.[14]

The FDA and CDC's National Youth Tobacco Survey showed that in 2021 the Vuse brand was the second most popular e-cigarette brand with youth, used by 10.5% of kids, amounting to 200,000 users.[15] (Puff Bar was more popular, but it now claims to use synthetic nicotine so it may not be considered a "tobacco product" regulated by the FDA Center for Tobacco Products.)

The TPL recognizes Vuse's popularity with kids, but downplays it: "the proportion of reported youth use of the brand 'Vuse' significantly increased from 2019 (1.2%) to 2020 (7.3%).[16] By 2021, 10.5% of kids and 10.8% of high school students were using Vuse, a 50% increase over 2020.[17] FDA did not discuss the 2021 data.

The TPL also stated, "However, the study did not specify the type of Vuse-branded products or the flavor used by youth, so it is *uncertain whether use of Vuse Solo products increased among youth* [emphasis added]." The TPL *assumes* that the increase in Vuse brand popularity does not apply to Vuse Solo tobacco flavor. This is one of many examples of FDA

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[14] 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. Available: https://pubmed.ncbi.nlm.nih.gov/32674965/

[15] Park-Lee E, Ren C, Sawdey MD, Gentzke AS, Cornelius M, Jamal A, Cullen KA. Notes from the Field: E-Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2021. MMWR Morb Mortal Wkly Rep. 2021 Oct 1;70(39):1387-1389. doi: 10.15585/mmwr.mm7039a4. PMID: 34591834; PMCID: PMC8486384. Available: https://pubmed.ncbi.nlm.nih.gov/34591834/

[16] Miech R, Leventhal A, Johnston L, O'Malley PM, Patrick ME, Barrington-Trimis J. Trends in Use and Perceptions of Nicotine Vaping Among US Youth From 2017 to 2020. JAMA Pediatr. 2021 Feb 1;175(2):185-190. doi: 10.1001/jamapediatrics.2020.5667. Erratum in: JAMA Pediatr. 2021 Mar 1;175(3):328. PMID: 33320241; PMCID: PMC7739194. Available: https://pubmed.ncbi.nlm.nih.gov/33320241/

[17] Youth-friendly "skins" are being sold for Vuse Solo. See https://www.google.com/search?q=vuse+solo+vs+vuse+alto&sxsrf=AOaemvLGKaqYOY03_vSwBVjIYZ3qXBSLlA:1639081195858&source=lnms&tbm=shop&sa=X&ved=2ahUKEwiZx76jxdf0AhU-LTQIHSn8CXoQ_AUoAXoECAEQAw&cshid=1639081247270892&biw=1434&bih=717&dpr=1.25

giving RJR the benefit of the doubt. In fact, the FDA has brand-specific data on flavors for specific brands of e-cigarettes from the NYTS, but did not use that information in its TPL or yet release the data to the scientific community or the public.

In any event, the popularity of the brand in general is more appropriate to consider than the popularity of a single line extension. For example, one would not say Marlboro's popularity in general does not apply to Marlboro menthol.

FDA misstates the evidence showing that youth e-cigarette use stimulates cigarette smoking

Perhaps FDA's most egregious failure in its scientific review is the statement, "Overall, the available evidence to date does not adequately address whether new product use in youth and young adults leads to regular smoking" (TPL page 18).

This statement is simply wrong.

There are at least 17 studies on the effect of e-cigarette use on subsequent cigarette smoking. ***Every one of these studies*** shows e-cigarette use increases the risk of cigarette smoking, further demonstrating why the marketing of Vuse Solo would not benefit the health of the population as a whole. Once they start, kids have 3-6 times the odds of going on to add cigarettes to e-cigarette use[18] with the newer studies[19] not included in these meta-analyses showing even higher risks.

Specifically addressing the FDA's erroneous statement, there is direct evidence – from the FDA's own PATH study – that initiating nicotine use with e-cigarettes ***triples*** the odds of

[18] 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. Available: https://pubmed.ncbi.nlm.nih.gov/32156694/
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. Available: https://pubmed.ncbi.nlm.nih.gov/34495974/

[19] Staff J, Kelly BC, Maggs JL, Vuolo M. Adolescent electronic cigarette use and tobacco smoking in the Millennium Cohort Study. Addiction. 2021 Jul 19. doi: 10.1111/add.15645. Epub ahead of print. PMID: 34286880. Available: https://pubmed.ncbi.nlm.nih.gov/34286880/
Martinelli T, Candel MJJM, de Vries H, Talhout R, Knapen V, van Schayck CP, Nagelhout GE. Exploring the gateway hypothesis of e-cigarettes and tobacco: a prospective replication study among adolescents in the Netherlands and Flanders. Tob Control. 2021 Jul 5:tobaccocontrol-2021-056528. doi: 10.1136/tobaccocontrol-2021-056528. Epub ahead of print. PMID: 34226262. Available: https://pubmed.ncbi.nlm.nih.gov/34226262/
Hair EC, Kreslake JM, Mowery P, Pitzer L, Schillo B, Vallone DM. A longitudinal analysis of e-cigarette use and cigar, little cigar or cigarillo initiation among youth and youth adults: 2017-2019. Drug Alcohol Depend. 2021 Sep 1;226:108821. doi: 10.1016/j.drugalcdep.2021.108821. Epub 2021 Jun 23. PMID: 34218009. Available: https://pubmed.ncbi.nlm.nih.gov/34218009/

eventually becoming a daily cigarette smoker.[20] The FDA also ignored the 2020 meta-analysis[21] that showed that ever using e-cigarettes by youth more than doubled the odds of later current smoking (OR 2.21, 95% CI 1.72-2.84; Figure S2). This result was confirmed in a more recent meta-analysis[22] of all available longitudinal studies (Figure 1).

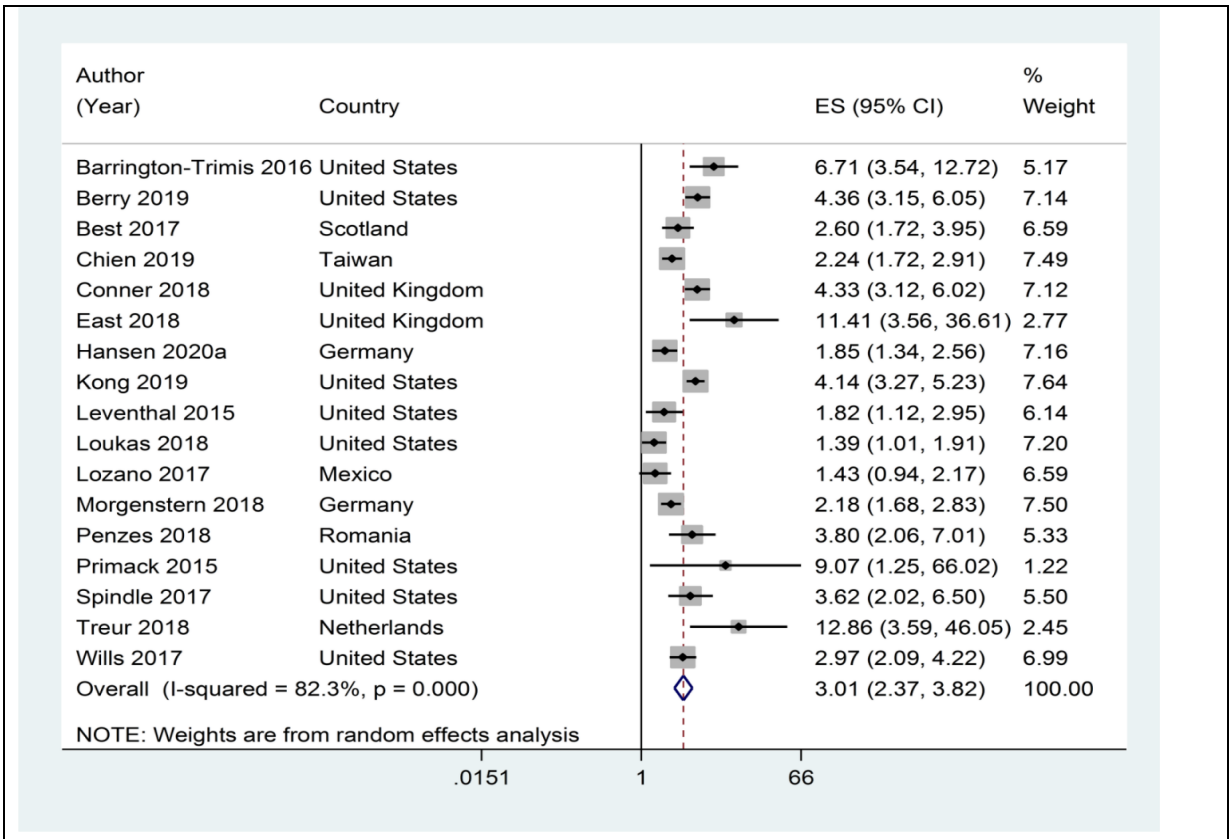

Figure 1. All the longitudinal studies show that among youth who had never smoked a cigarette at baseline, e-cigarette use elevated the relative risk of smoking at follow-up. Combining all the studies the adjusted risk ratios for cigarette smoking was about tripled (ever smoking: OR 3.01, 95% CI: 2.37 to 3.82; p<0·001; current smoking: OR 2.56, 95% CI: 1.61 to 4.07; p<0·001, not shown) at follow up. Source: Yoong, et al, 2021

[20] Pierce JP, Chen R, Leas EC, White MM, Kealey S, Stone MD, Benmarhnia T, Trinidad DR, Strong DR, Messer K. Use of E-cigarettes and Other Tobacco Products and Progression to Daily Cigarette Smoking. Pediatrics. 2021 Feb;147(2):e2020025122. doi: 10.1542/peds.2020-025122. Epub 2021 Jan 11. PMID: 33431589; PMCID: PMC7849197. Available: https://pubmed.ncbi.nlm.nih.gov/33431589/

[21] 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. Available: https://pubmed.ncbi.nlm.nih.gov/32156694/

[22] 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. Available: https://pubmed.ncbi.nlm.nih.gov/34495974/

Youth smoking does not need to be "regular" to predict long-term use. Past 30-day adolescent smoking is a strong predictor of young adult established smoking years later.[23] There is a strong dose-response relationship between past 30-day smoking in adolescence-even a single day in the month-and 30-day and daily smoking in young adulthood.

E-cigarettes are expanding the youth tobacco epidemic

When considering whether to grant a marketing order, FDA must consider[24] whether the marketing of the proposed product will increase or decrease the likelihood that youth and other non-users will start using tobacco products and the increased or decreased likelihood that current smokers will stop smoking. However, in considering the Vuse Solo PMTA, FDA ignored the very strong and consistent evidence that e-cigarettes are expanding the tobacco epidemic by ***attracting large numbers of youth who are at low risk of initiating nicotine use with cigarettes***.[25]

These low-risk youth are not using e-cigarettes *instead of* cigarettes. The increases in youth e-cigarette use are much larger than the decline in youth cigarette use, resulting in an increase in total tobacco product consumption (Figure 2).

[23] Dutra LM, Glantz SA. Thirty-day smoking in adolescence is a strong predictor of smoking in young adulthood. Prev Med. 2018 Apr;109:17-21. doi: 10.1016/j.ypmed.2018.01.014. Epub 2018 Feb 3. PMID: 29366819; PMCID: PMC5922790.Available: https://pubmed.ncbi.nlm.nih.gov/29366819/

[24] Family Smoking Protection and Tobacco Control Act section 910(c)(4).

[25] Creamer MR, Dutra LM, Sharapova SR, Gentzke AS, Delucchi KL, Smith RA, Glantz SA. Effects of e-cigarette use on cigarette smoking among U.S. youth, 2004-2018. Prev Med. 2021 Jan;142:106316. doi: 10.1016/j.ypmed.2020.106316. Epub 2020 Nov 30. PMID: 33272598; PMCID: PMC7796895. Available: https://pubmed.ncbi.nlm.nih.gov/33272598/

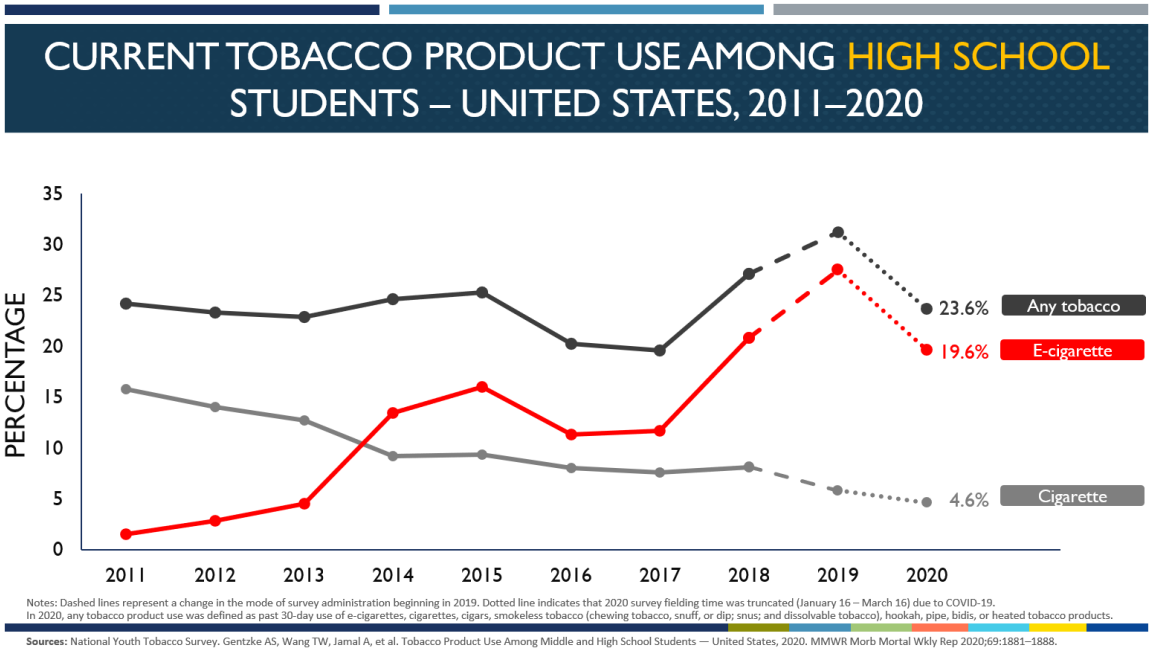

Figure 2. E-cigarette use and total tobacco use have dramatically increased among high school seniors, with e-cigarette use increasing much more and faster than cigarette use declined. Source: CDC.

Consistent with these findings, the upswing in youth e-cigarette use was also associated with a slowing in the decline of current youth cigarette smoking.[26] Thus, the evidence suggests that the marketing of Vuse, like e-cigarettes in general, will increase the likelihood that non-users, including youth who are at low risk of initiating nicotine use, will initiate with Vuse and decrease the likelihood that cigarette smokers will stop smoking.

FDA places heavy weight on the assumption that prohibiting flavors (other than menthol) will deter kids from using Vuse

The FDA TPL states, "Although the new products are not pod mods, they are sleek and small in design, user friendly cartridge-based, and easily rechargeable**. *Although there is some risk of youth uptake of these products, in general, tobacco-flavored ENDS are less appealing to youth compared to non-tobacco flavored ENDS, making the risk of youth initiation low for these products."*** (TPL page 17).

This statement assumes that the numerous youth-friendly features of the product (sleek and small design, user friendly, easy to charge) will be outweighed by the product's tobacco-flavor (as opposed to youth-attractive menthol/mint, candy- or fruit-flavors). Multiple product features contribute to youth appeal. In addition, the assumption that tobacco flavor renders the

[26] Creamer MR, Dutra LM, Sharapova SR, Gentzke AS, Delucchi KL, Smith RA, Glantz SA. Effects of e-cigarette use on cigarette smoking among U.S. youth, 2004-2018. Prev Med. 2021 Jan;142:106316. doi: 10.1016/j.ypmed.2020.106316. Epub 2020 Nov 30. PMID: 33272598; PMCID: PMC7796895. Available: https://pubmed.ncbi.nlm.nih.gov/33272598/

product unattractive to youth could prove to be invalid, particularly if FDA allows menthol Vuse and other e-cigarettes. Several studies provide direct evidence that if flavors are banned but menthol flavored e-cigarettes remain available, youth will simply shift from other flavors to menthol.

- A national study[27] using Nielsen retailer scanner data of Juul's November 2018 decision to limit the flavors it sold in stores (but not on its website) to menthol, mint and tobacco found that after Juul withdrew fruit and sweet flavors from stores, menthol/mint came to dominate the e-cigarette market and in 2019, a new surge in fruit-flavor sales by non-Juul brands occurred. After a decline in sales following Juul's decision to withdraw some flavored products from stores, Juul sales recovered within weeks and surpassed their previous maximum in those same channels, as consumption shifted to the menthol/mint and tobacco flavors.
- A study of Connecticut high school students[28] found similar results: Use of the restricted flavors dropped, while mint pod use increased. Tobacco and menthol pod use remained stable.
- Another study[29] of what happened after Juul stopped selling all flavors but tobacco and menthol in 2019 and FDA issued its 2020 e-cigarette flavor guidance prohibiting sale of flavored cartridge-based products, sales simply shifted to menthol. Using Nielsen Retail Scanner data from September 2013 to March 2020 revealed that Juul's removal of mint products was followed by a 59.4% increase in the market share of menthol e-cigarettes over 4 weeks. The FDA's 2020 guidance was followed by a 54.5% increase in market share of menthol-flavored e-cigarettes over 4 weeks and a 82.8% increase over 8 weeks.
- In the 2021 NYTS, 46% of users of flavored cartridge-based products reported using menthol-flavored products.[30]

The fact that FDA explicitly did not act on the Vuse menthol PMTA and that it has granted marketing orders[31] for Philip Morris' menthol IQOS products and four US Tobacco menthol smokeless products raises serious concerns that menthol e-cigarettes will be authorized. (Director Zeller has stated that menthol in e-cigarettes raised "unique considerations,"[32] but has

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[27] Liber A, Cahn Z, Larsen A, Drope J. Flavored E-Cigarette Sales in the United States Under Self-Regulation From January 2015 Through October 2019. Am J Public Health. 2020 Jun;110(6):785-787. doi: 10.2105/AJPH.2020.305667. Epub 2020 Apr 16. PMID: 32298169; PMCID: PMC7204483. Available: https://pubmed.ncbi.nlm.nih.gov/32298169/

[28] Morean ME, Bold KW, Kong G, Camenga DR, Jackson A, Simon P, Davis DR, Krishnan-Sarin S. High school students' use of JUUL pod flavors before and after JUUL implemented voluntary sales restrictions on certain flavors in 2018. PLoS One. 2020 Dec 15;15(12):e0243368. doi: 10.1371/journal.pone.0243368. PMID: 33320885; PMCID: PMC7737969. Available: https://pubmed.ncbi.nlm.nih.gov/33320885/

[29] Diaz MC, Donovan EM, Schillo BA, Vallone D. Menthol e-cigarette sales rise following 2020 FDA guidance. Tob Control. 2021 Nov;30(6):700-703. doi: 10.1136/tobaccocontrol-2020-056053. Epub 2020 Sep 23. PMID: 32967985. Available: https://pubmed.ncbi.nlm.nih.gov/32967985/

[30] Park-Lee E, Ren C, Sawdey MD, Gentzke AS, Cornelius M, Jamal A, Cullen KA. Notes from the Field: E-Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1387-1389

[31] FDA. Premarket Tobacco Product Marketing Granted Orders. https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders. Accessed 7 Dec 2021.

[32] Hammond H. CTP Director Gives Update on Proposed Menthol Ban. CSP. Dec. 06, 2021. Available: https://www.cspdailynews.com/tobacco/ctp-director-gives-update-proposed-menthol-ban

not explained what those unique considerations are. In contrast, the studies cited above indicate that menthol in e-cigarettes is functioning similarly to menthol in cigarettes. Based on history, it is likely that RJR (and other companies) can replace other flavors with menthol through effective marketing and changing the names of the flavors to "concept flavors" such as "Lush Ice."[33]

FDA ignored the consistent evidence that e-cigarettes as consumer products do not help smokers quit

Another key erroneous statement the FDA makes is that "The extent to which the new products (or ENDS [electronic nicotine delivery systems, i.e., e-cigarettes] in general) facilitated cessation was unknown" (TPL page 13).

This statement is also simply wrong.

Both a 2020 meta-analysis[34] (not cited by the FDA) based on 55 population observational studies as well as a 2021 one[35] based on 26 population cohort studies find that e-cigarettes used as consumer products in the real world (what the FDA Center for Tobacco Products regulates) are ***not associated with increased smoking cessation***.

The new 2021 meta-analysis[36] is particularly relevant because it limited the studies to cohort (longitudinal) studies that follow people forward in time, precisely the kind of studies that the FDA said it prioritized. (The 2020 meta-analysis[37] considered both cohort and cross-sectional studies; analyzing them separately showed no significant difference in the results.)

Moreover, another meta-analysis[38] found that adults who use e-cigarettes double the odds of relapse to smoking, a result reinforced in a recent study[39] using the FDA's own PATH dataset that followed smokers who quit with e-cigarettes forward in time.

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[33] Gaiha, Shivani Mathur, et al. "E-cigarette Devices, Brands and Flavors Attract Youth: Informing FDA's Policies and Priorities to Close Critical Gaps." Addictive Behaviors (2021): 107179.

[34] 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. Available: https://pubmed.ncbi.nlm.nih.gov/33351653/

[35] 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. Available: https://pubmed.ncbi.nlm.nih.gov/34712864/

[36] 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. Available: https://pubmed.ncbi.nlm.nih.gov/34712864/

[37] 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. Available: https://pubmed.ncbi.nlm.nih.gov/33351653/

[38] Barufaldi LA, Guerra RL, de Albuquerque RCR, Nascimento A, Chança RD, de Souza MC, de Almeida LM. Risk of smoking relapse with the use of electronic cigarettes: A systematic review with meta-analysis of longitudinal studies. Tob Prev Cessat. 2021 Apr 27;29:29. doi: 10.18332/tpc/132964. PMID: 33928198; PMCID: PMC8078138. Available: https://pubmed.ncbi.nlm.nih.gov/33928198/

[39] Pierce JP, Chen R, Kealey S, Leas EC, White MM, Stone MD, McMenamin SB, Trinidad DR, Strong DR, Benmarhnia T, Messer K. Incidence of Cigarette Smoking Relapse Among Individuals Who Switched to e-Cigarettes or Other Tobacco Products. JAMA Netw Open. 2021 Oct 1;4(10):e2128810. doi:

Despite these facts and incomplete information in the RJR PMTA application for Vuse Solo, (as reported by FDA; the PMTA is not made publicly available) FDA nevertheless concluded that Vuse Solo would help smokers quit:

> The extent to which the new products (or ENDS [e-cigarettes] in general) facilitated cessation was unknown, and therefore the conclusion made by the applicant that the availability of flavors may help smokers completely switch was unsupported by the data. *The applicant used longitudinal studies to examine tobacco use transitions from exclusive cigarette smoking to exclusive ENDS use [i.e., quitting cigarettes] in the first cycle review.* Rates of switching from combusted cigarette use to exclusive ENDS use reported in the application (1.5-6.7%) were comparable to rates in the published literature (3.4-5.9%).[27-29] However, the applicant did not provide information that examined the role of flavors on tobacco use transitions. Additionally, *the applicant did not provide evidence on tobacco use transitions overall or the role of flavors on tobacco use transitions for cycle 2 of PMTA review. In the absence of product-specific (longitudinal) data on switching in this PMTA, it may be reasonable to infer that switching rates for this product would be somewhere within the range found in the published literature and presented in the PMTA.* However, based on the applicant's analysis and available evidence showing higher preference of original flavored ENDS among adult smokers, *the new products could help current adult smokers in quitting or reducing cigarette smoking.* (TPL page 13).

Despite the fact that RJR's own data showed that 93.3% to 98.5% of Vuse users did not "switch completely," FDA's health assessment assumed that smokers would "switch completely."

In addition, rather than requiring specific evidence that, unlike e-cigarettes in general, Vuse Solo had a specific cessation benefit, the FDA relied on the existing literature and *assumed* Vuse Solo would have a similar benefit as e-cigarettes in general.

None of the three studies the FDA TPL cites clearly address the effects of e-cigarette use on smoking cessation.

- Reference 27[40] simply concluded "This study suggests that e-cigarette use patterns are highly variable over a 1-year period."
- Reference 28[41] concluded, "This research suggests that dual use of combustible and e-cigarettes is not a sustained pattern for the majority of dual users, but it is more likely to be a continued pattern if the user is more dependent on e-cigarettes."

10.1001/jamanetworkopen.2021.28810. PMID: 34665239; PMCID: PMC8527352. Available: https://pubmed.ncbi.nlm.nih.gov/34665239/

[40] Coleman B, Rostron B, Johnson SE, Persoskie A, Pearson J, Stanton C, Choi K, Anic G, Goniewicz ML, Cummings KM, Kasza KA, Silveira ML, Delnevo C, Niaura R, Abrams DB, Kimmel HL, Borek N, Compton WM, Hyland A. Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013-2015). Tob Control. 2019 Jan;28(1):50-59. doi: 10.1136/tobaccocontrol-2017-054174. Epub 2018 Apr 25. PMID: 29695458; PMCID: PMC6202279. Available: https://pubmed.ncbi.nlm.nih.gov/29695458/

[41] Piper ME, Baker TB, Benowitz NL, Jorenby DE. Changes in Use Patterns Over 1 Year Among Smokers and Dual Users of Combustible and Electronic Cigarettes. Nicotine Tob Res. 2020 Apr 21;22(5):672-680. doi:

- Reference 29[42] concluded, "[Youth] Ever-ENDS use predicts future cigarette smoking, and frequency of ENDS use has a differential impact on subsequent cigarette smoking uptake or reduction."

It is not clear why the FDA selected these three studies while ignoring the much larger and more relevant literature showing ***no cessation benefit and increased relapse risk***. Here are the conclusions from the meta-analyses which were based on much larger studies (and more current) data:

- "As consumer products, in observational studies, e-cigarettes were not associated with increased smoking cessation in the adult population. …E-cigarettes should not be approved as consumer products …"[43] (Wang et al, 2020)
- "We did not find quality evidence for an association between e-cigarette use and smoking cessation."[44] (Hedman et al, 2021) (Figure 3)
- "Considering the growing popularity of e-cigarettes among former smokers, our results point to the great potential for an increase in the frequency of relapse to conventional smoking and vaping for those who move to regular use of e-cigarettes."[45] (Barufaldi et al, 2021)

10.1093/ntr/ntz065. Erratum in: Nicotine Tob Res. 2020 Oct 8;22(10):1934. PMID: 31058284; PMCID: PMC7457322. Available: https://pubmed.ncbi.nlm.nih.gov/31058284/

[42] Stanton CA, Bansal-Travers M, Johnson AL, Sharma E, Katz L, Ambrose BK, Silveira ML, Day H, Sargent J, Borek N, Compton WM, Johnson SE, Kimmel HL, Kaufman AR, Limpert J, Abrams D, Cummings KM, Goniewicz ML, Tanski S, Travers MJ, Hyland AJ, Pearson JL. Longitudinal e-Cigarette and Cigarette Use Among US Youth in the PATH Study (2013-2015). J Natl Cancer Inst. 2019 Oct 1;111(10):1088-1096. doi: 10.1093/jnci/djz006. PMID: 30689915; PMCID: PMC6792095. Available: https://pubmed.ncbi.nlm.nih.gov/30689915/

[43] 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. Available: https://pubmed.ncbi.nlm.nih.gov/33351653/

[44] 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. Available:

[45] Barufaldi LA, Guerra RL, de Albuquerque RCR, Nascimento A, Chança RD, de Souza MC, de Almeida LM. Risk of smoking relapse with the use of electronic cigarettes: A systematic review with meta-analysis of longitudinal studies. Tob Prev Cessat. 2021 Apr 27;29:29. doi: 10.18332/tpc/132964. PMID: 33928198; PMCID: PMC8078138. Available: https://pubmed.ncbi.nlm.nih.gov/33928198/

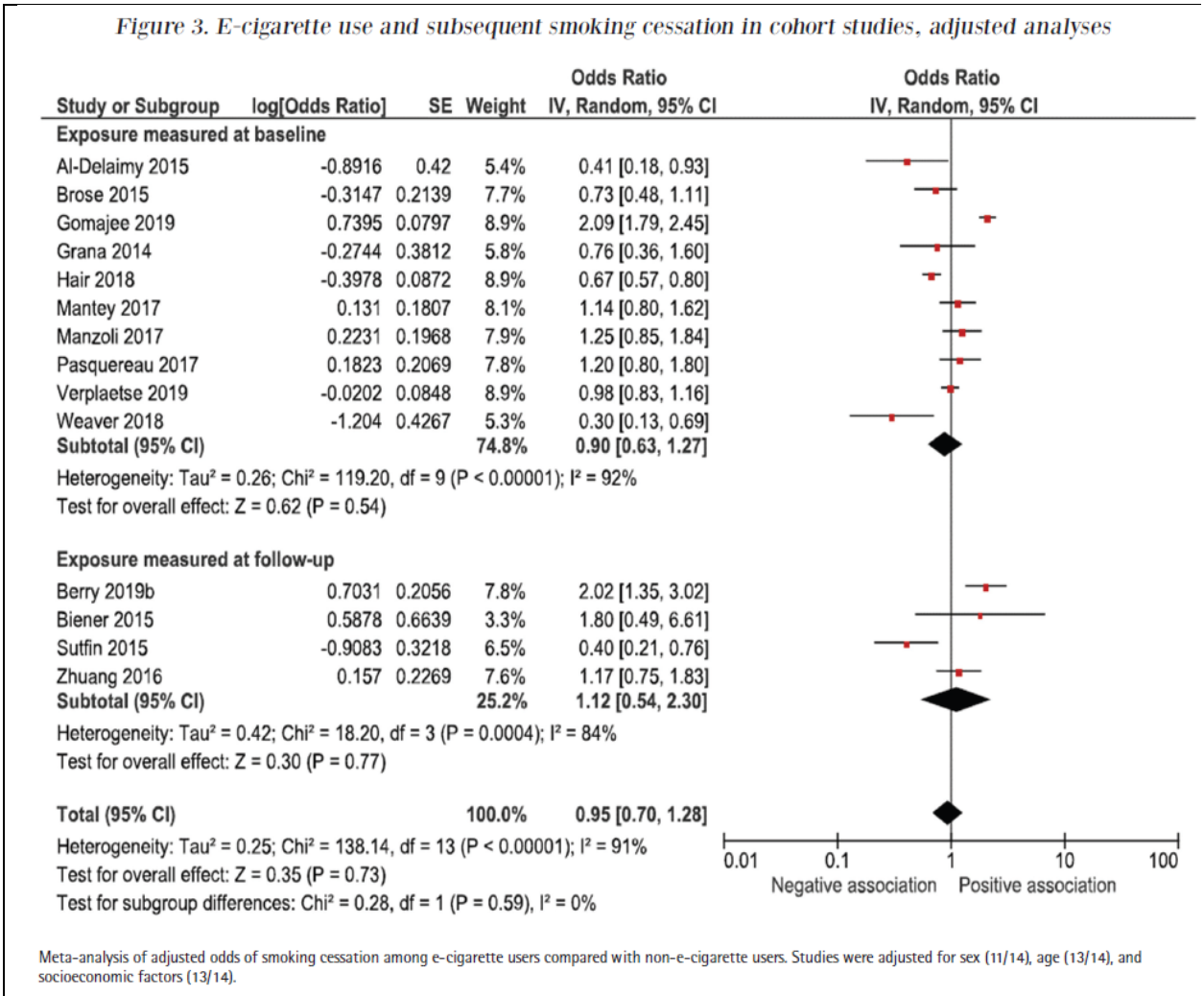

Figure 3. E-cigarette use has no detectable effect on smoking cessation in cohort (longitudinal) studies. The overall odds ratio for quitting is 0.95 (95% CI 0.70-1.28; p=0.73), which is indistinguishable from 1.0 (no effect). Among all the studies in this meta-analysis only 2 showed significant increases in cessation compared to 3 that showed significant depression in cessation. All the others showed no significant effect. Source: Hedman, et al 2021.

Indeed, Hon Lik, the Chinese pharmacist from Shenyang in northeast China who is credited[46] with inventing the modern e-cigarette in 2003 as a smoking cessation device was still smoking in 2021.[47] Even he did not "switch completely."

[46] In fact, Philip Morris had developed a functioning e-cigarette by the mid-1990s as part of an effort to hold on to customers who might otherwise quit nicotine but chose not to take it to market. Dutra LM, Grana R, Glantz SA. Philip Morris research on precursors to the modern e-cigarette since 1990. Tob Control. 2017 Dec;26(e2):e97-e105. doi: 10.1136/tobaccocontrol-2016-053406. Epub 2016 Nov 15. PMID: 27852893; PMCID: PMC5432409. Available: https://pubmed.ncbi.nlm.nih.gov/27852893/

[47] Spencer B, Calver T. Vape nation: how did Britain end up so hooked on e- cigarettes? England is an outlier in promoting vaping as a safe alternative to smoking. Other countries are far from convinced. The Sunday Times. October 30 2021. Available: https://www.thetimes.co.uk/article/vape-nation-how-did-britain-end-up-so-hooked-on-e-cigarettes-q5r5vg89s

The fact that the literature shows lack of a benefit on smoking cessation – and increased relapse risk – means that there is no benefit to trade off against the thousands of kids being recruited to nicotine addiction. These two facts alone should have made it impossible to justify a decision to authorize e-cigarette continued marketing as appropriate for the protection of public health.

FDA does not address the appeal of Vuse Solo to adult nonsmokers

The FDA noted, "The applicant study findings indicate that among most adult non-tobacco users, both former (84.3%) and never users (74.7%), indicated they were not interested in the new products" and accepts RJR's conclusion "that adult never users are not likely to become users on the new products" (TPL page 16). An alternative reading of these observations is that 15.7% of former adult smokers and 25.3% of adult never smokers *were* interested in Vuse Solo. The FDA does not address the fact that there is no public health benefit of recreational e-cigarette use for adult non-tobacco users.

In addition to effects on youth, Vuse's potential to promote relapse among former smokers and attract never smokers must be included in a quantitative assessment of the net public health impact of authorizing the sale of Vuse Solo.

FDA's discussion of health effects wrongly focuses on reducing the levels of a few cigarette toxins, but fails to consider other toxins or the large literature demonstrating a wide range of adverse physiological effects

The discussion of toxicity and health effects puts a great deal of emphasis on the FDA's Harmful and Potentially Harmful Constituents (HPHC) list. While it is fine to present the HPHC comparisons, it is important to emphasize that this list is narrow in scope, focused mainly on combustion products and carcinogens. This tunnel vision is an important limitation because heart and lung disease kill more smokers than cancer, and the current HPHC list does not include many cardiovascular and pulmonary toxins. In 2019 FDA proposed[48] a well-justified[49] expanded HPHC list that addresses this problem that is awaiting finalization.

Propylene glycol (PG) and glycerol (also known as glycerin, vegetable glycerin, or VG) are ingredients found in Vuse Solo that FDA considered to be harmful constituents on their proposed updated list. Despite evidence that FDA cited in its proposed update to the HPHC list[50]

[48] FDA. Notice: Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments. Publication Date: 08/05/2019. Document Citation: 84 FR 38032 Page 38032-38035. Docket No. FDA-2012-N-0143. Document Number: 2019-16658. Available: https://www.federalregister.gov/documents/2019/08/05/2019-16658/harmful-and-potentially-harmful-constituents-in-tobacco-products-established-list-proposed-additions

[49] Lempert LK, St.Helen G, Gotts J, Kozlovich S, Springer M, Halpern-Felsher B, Glantz SA. . UCSF TCORS public comment on expansion of FDA HPHC list. October 2, 2019. Regulations.gov tracking number 1k3-9cij-8wgr. Available: https://tobacco.ucsf.edu/ucsf-tcors-public-comment-expansion-fda-hphc-list

[50] FDA. Notice: Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments. Publication Date: 08/05/2019. Document Citation: 84 FR 38032 Page 38032-38035. Docket No. FDA-2012-N-0143. Document Number: 2019-16658. Available: https://www.federalregister.gov/documents/2019/08/05/2019-16658/harmful-and-potentially-harmful-constituents-in-tobacco-products-established-list-proposed-additions

(and subsequent published research[51]), PG and VG have adverse health effects FDA did not comment on the risks associated with these constituents in the Vuse Solo TPL.

Rather, the FDA drew sweeping toxicological conclusions based on very limited evidence and despite the fact that RJR did not assess dual use that "would be much more likely to occur in real-world conditions (TPL pages 25-26):

> ***Per the toxicology review, the new products' aerosols are significantly less toxic than the combusted tobacco comparisons based on available nonclinical, HPHC, and BOE data.*** Per the BCP review, short-term (five days) switching from cigarette smoking to the new products resulted in significant reductions in the urinary and blood BOE. Per the medical review, the numbers of AEs were generally low and mostly mild and transient in short-term clinical studies. ***However, the applicant's switching studies did not assess the effects of long-term use and the impact of dual use which would be more likely to occur in real-world conditions.***
>
> There is limited data about the long-term health effects of ENDS from large clinical studies or long-term epidemiological studies. In addition, the study design limitations (e.g., small sample size, generally healthy participants, short exposure periods) in the published literature make it difficult to draw definitive conclusions related to health effects of ENDS, specifically the new products. ***Therefore, the long-term health effects and potential short and long-term health effects from dual use could not be evaluated***. However, based on available information, I agree that adult smokers who switch to these products (either completely or with a significant reduction in cigarette consumption) would benefit from reduced exposure to many HPHCs. ***While the effects of dual use were not assessed, significant reductions in systemic exposures after short-term switching and the available evidence suggest that daily use of the new products with concomitant reduction in CPD may provide health benefits from a harm reduction***

[51] There are a large number of papers documenting a range of adverse effects of PG/VG in e-cigarette aerosol. Here are a few recent papers:
Jabba SV, Diaz AN, Erythropel HC, Zimmerman JB, Jordt SE. Chemical Adducts of Reactive Flavor Aldehydes Formed in E-Cigarette Liquids Are Cytotoxic and Inhibit Mitochondrial Function in Respiratory Epithelial Cells. Nicotine Tob Res. 2020 Dec 15;22(Suppl 1):S25-S34. doi: 10.1093/ntr/ntaa185. PMID: 33320255; PMCID: PMC8224836. Available: https://pubmed.ncbi.nlm.nih.gov/33320255/
Ghosh A, Coakley RC, Mascenik T, Rowell TR, Davis ES, Rogers K, Webster MJ, Dang H, Herring LE, Sassano MF, Livraghi-Butrico A, Van Buren SK, Graves LM, Herman MA, Randell SH, Alexis NE, Tarran R. Chronic E-Cigarette Exposure Alters the Human Bronchial Epithelial Proteome. Am J Respir Crit Care Med. 2018 Jul 1;198(1):67-76. Doi: 10.1164/rccm.201710-2033OC. PMID: 29481290; PMCID: PMC6034122. Available: https://pubmed.ncbi.nlm.nih.gov/29481290/
Jin L, Lynch J, Richardson A, Lorkiewicz P, Srivastava S, Theis W, Shirk G, Hand A, Bhatnagar A, Srivastava S, Conklin DJ. Electronic cigarette solvents, pulmonary irritation, and endothelial dysfunction: role of acetaldehyde and formaldehyde. Am J Physiol Heart Circ Physiol. 2021 Apr 1;320(4):H1510-H1525. Doi: 10.1152/ajpheart.00878.2020. Epub 2021 Feb 5. PMID: 33543686; PMCID: PMC8260384. Available: https://pubmed.ncbi.nlm.nih.gov/33543686/
Beklen A, Uckan D. Electronic cigarette liquid substances propylene glycol and vegetable glycerin induce an inflammatory response in gingival epithelial cells. Hum Exp Toxicol. 2021 Jan;40(1):25-34. doi: 10.1177/0960327120943934. Epub 2020 Jul 30. PMID: 32729321. Available: https://pubmed.ncbi.nlm.nih.gov/32729321/

perspective in terms of reducing exposure to HPHCs relative to continued use of cigarette smoking alone.

This conclusion is based on speculation, not evidence.

E-cigarettes deliver thousands of toxins different from cigarettes, and have pulmonary and cardiac toxicity in addition to cancer risk

Moving beyond the limited consideration of currently listed HPHC's is particularly important in light of the fact that e-cigarettes deliver thousands of toxins[52] with a risk profile *different* from cigarettes. The toxic load e-cigarette impose is not simply a subset of cigarette toxins.[53]

The FDA failed to engage the large biological literature[54] indicating that e-cigarettes have substantial pulmonary and cardiac toxicity, often with different effects or with adverse effects as large as in combusted cigarettes.

For example, the FDA did not address a 2021 review of 106 papers, "Cardiorespiratory and Immunologic Effects of Electronic Cigarettes,"[55] that explains why just avoiding the combustion products in conventional cigarettes does not mean that e-cigarettes are safer than cigarettes:

> Because e-cigarettes do not burn tobacco, and because they generate lower levels of combustion products than conventional cigarettes [7], some believe that e-cigarettes are a safer alternative to combustible cigarettes, and that they could aid smoking cessation among those who will not, or cannot quit smoking [8]. The full inventory of the chemicals generated by combustible cigarettes exceeds several thousand. Some of these chemicals are highly poisonous and toxic, and many incite or promote carcinogenesis, cardiovascular injury, and pulmonary damage [9]. ***Hence, it seems reasonable to expect that nicotine, without reactive chemicals, must be less toxic than nicotine delivered with a mixture of combustion-generated toxins.*** This expectation derives the oft-repeated mantra that "people smoke for nicotine, but they die from tar" [10]. And from it, it follows that if all the tar (as well as other combustion products) were removed, inhaling nicotine will be much safer. ***Unfortunately, for many reasons, the situation is more complicated than expected.***

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[52] 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 18;34(10):2216-2226. doi: 10.1021/acs.chemrestox.1c00253. Epub 2021 Oct 5. PMID: 34610237. Available: https://pubmed.ncbi.nlm.nih.gov/34610237/

[53] Terry Gordon, Emma Karey, Meghan E. Rebuli, Yael Escobar, Ilona Jaspers, Lung Chi Chen. E-Cigarette Toxicology Annual Review of Pharmacology and Toxicology 2022 62:1. Available: https://www.annualreviews.org/doi/10.1146/annurev-pharmtox-042921-084202

[54] Several papers are summarized at https:\\\profglantz.com\2021\10\25\science-fda-and-everyone-else-needs-to-actively-engage-as-they-think-about-whether-to-authorize-juul-and-the-other-ecigs

[55] Keith R, Bhatnagar A. Cardiorespiratory and Immunologic Effects of Electronic Cigarettes. Curr Addict Rep. 2021 Mar 5:1-11. doi: 10.1007/s40429-021-00359-7. Epub ahead of print. PMID: 33717828; PMCID: PMC7935224. Available: https://pubmed.ncbi.nlm.nih.gov/33717828/

First, avoiding combustion does not remove all noxious chemicals. Although e-cigarettes do not form high levels of strongly carcinogenic benzopyrenes and tobacco-specific nitrosamines, heating mixtures of nicotine and propylene glycol and vegetable glycerin (PG:VG) in e-cigarettes generates reactive carbonyls such as formaldehyde, acetaldehyde, and acrolein [11–14], which have been variably linked to carcinogenesis [15] , cardiovascular injury [16, 17], and increased risk of cardiovascular disease [18]. The generation of carbonyls from e-cigarettes varies with use patterns, e-liquid ingredients, and operating conditions [19], and even though the extent of carbonyl generation by e-cigarettes is generally lower than by combustible cigarettes, daily carbonyl exposure from e-cigarettes could still exceed exposure limits [20].

Second, e-cigarette aerosols sporadically contain metals (Fe, Ni, Cu, Cr, Zn, Pb), generated by the heating coil [21], which could add to the toxicity of the aerosol.

Third, like combustible cigarettes, e-cigarettes produce aerosols that contain fine and ultrafine particles [22], which can trigger cardiovascular events and promote the progression of pulmonary and cardiovascular disease [23]. Finally, a direct comparison of the relative toxicity of e-cigarettes and combustible cigarettes may not be entirely meaningful. Toxicity due to a chemical, drug, or exposure depends upon its dose. Therefore, even though per puff, e-cigarettes may generate lower levels of toxins; their toxicity may approach that of combustible cigarettes if the use of e-cigarettes (exposure/dose) is higher than that of combustible cigarettes. For instance, if e-cigarettes are half as harmful as combustible cigarettes, but are used twice as much, there would be little harm reduction by using e-cigarettes over combustible cigarettes. Therefore, for both e-cigarettes and combustible cigarettes, harm could be reduced only by reducing exposure. Here too, the relationship is not straightforward. ***The dose response relationship between smoking and ischemic heart disease, for instance, is non-linear. It shows that smoking just 3 cigarettes a day imparts 80% of the harm attributable to smoking 20–40 cigarettes per day [24•]. In other words, 85–92% reduction in exposure results in only 20% harm reduction.***

Therefore, reducing toxin exposure by using e-cigarettes may not result in proportional harm reduction. Indeed, as discussed below, ***recent evidence suggests that even though e-cigarettes generate lower levels of toxins than combustible cigarettes, their use may be associated with significant cardiorespiratory injury as well as immune dysregulation.*** [Emphasis added. Paragraph breaks added for readability. Citations are to reference list in the review paper.]

Continuing to focus on the outdated HPHC list is a serious problem that substantially increases the risk that FDA will miss important toxicities in new products.

The FDA mentions but does not act on its own study showing no overall mortality benefit of smoking reduction and fails to adequately address dual use

FDA improperly champions the health benefits of smoking reduction while largely ignoring the health impacts of dual use. As highlighted in Mitch Zeller's statement in the FDA

press release,[56] the FDA also saw ***smoking reduction*** as contributing to the public health benefits of authorizing Vuse Solo.

For this to be true, the FDA *assumes* dual use (smoking cigarettes and using e-cigarettes at the same time) would have to be safer than smoking, at least as long the number of cigarettes drops. On page 22 the TPL says:

> A recent study examining Waves 1 and 2 of the PATH data reported that participants with moderate to high reductions in CPD [cigarettes per day] had also lower levels of biomarkers. ***The impact of dual use on BOE [biomarkers of exposure, toxic chemicals detected in people using the product] levels and the associated health risks were not assessed; however, based on the currently available evidence, reducing CPD likely leads to less exposure to harmful toxicants than continued smoking and may help for eventual quitting***. [citations dropped]

But a few pages later (page 24) the TPL reports that dual users ***do have higher exposures to some toxins***:

> Some biomarker data from observational studies have also found that dual users can have higher levels of certain biomarkers of exposure than exclusive cigarette smokers.[53, 61] [citations refer to TPL reference list]

Specifically, TPL reference 53[57] concludes, "using combusted tobacco cigarettes alone or in combination with e-cigarettes is associated with higher concentrations of potentially harmful tobacco constituents in comparison with using e-cigarettes alone" and TPL reference 61[58] concludes, "Dual users of cigarettes with either e-cigarettes or smokeless tobacco are exposed to higher levels of certain toxicants and carcinogens than exclusive cigarette smokers."

Most important, the FDA's own research (TPL reference 62[59]) finds that there is ***no overall health benefit of reduction in the number cigarettes per day*** smoked:

> A meta-analysis found that compared to heavy smokers, dual users who are able to reduce the number of cigarettes they smoke by at least 50% had a significant reduction in

[56] https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-e-cigarette-products-marking-first-authorization-its-kind-agency

[57] Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J, Wang L, Christensen C, Ambrose B, Borek N, van Bemmel D, Konkel K, Erives G, Stanton CA, Lambert E, Kimmel HL, Hatsukami D, Hecht SS, Niaura RS, Travers M, Lawrence C, Hyland AJ. Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. JAMA Netw Open. 2018 Dec 7;1(8):e185937. doi: 10.1001/jamanetworkopen.2018.5937. PMID: 30646298; PMCID: PMC6324349. Available: https://pubmed.ncbi.nlm.nih.gov/30646298/

[58] Rostron BL, Corey CG, Chang JT, van Bemmel DM, Miller ME, Chang CM. Associations of Cigarettes Smoked Per Day with Biomarkers of Exposure Among U.S. Adult Cigarette Smokers in the Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013-2014). Cancer Epidemiol Biomarkers Prev. 2019 Sep;28(9):1443-1453. doi: 10.1158/1055-9965.EPI-19-0013. Epub 2019 Jun 25. PMID: 31239264; PMCID: PMC6726522. Available: https://pubmed.ncbi.nlm.nih.gov/31239264/

[59] 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 Mar 19;23(4):635-642. doi: 10.1093/ntr/ntaa156. PMID: 32803250. Available: https://pubmed.ncbi.nlm.nih.gov/32803250/

lung cancer risk.[62] However, ***reductions in cigarette smoking have not been found to lower the risk of all-cause mortality, all-cancer risk, or other smoking/tobacco-related cancers***.[62] (TPL page 24).

In addition, a meta-analysis of e-cigarette use and lung disease[60] not cited by FDA found increases in risk associated with e-cigarette use after controlling for smoking (i.e., among dual users):

> Epidemiological studies, both cross-sectional and longitudinal, show a significant association of e-cigarette use with asthma and COPD, controlling for cigarette smoking and other covariates. For asthma (n = 15 studies), the pooled adjusted odds ratio (AOR) was 1.39 (CI 1.28-1.51); for COPD (n = 9 studies) the AOR was 1.49 (CI 1.36-1.65).

Cross-sectional studies of e-cigarette use and heart disease[61] and erectile disfunction[62] also show increased risks of dual use.

While FDA often gave RJR the benefit of the doubt when failing to submit evidence, FDA discounts cross-sectional studies, even though such studies are routinely considered by other health authorities including the Surgeon General, saying: "As many of these studies utilized cross-sectional surveys to examine these relationships, the timing of ENDS use and disease onset cannot be established with certainty." At the same time, FDA ignored the longitudinal studies[63] https://pubmed.ncbi.nlm.nih.gov/33154031/in areas such as pulmonary disease.

Thus, the papers FDA cites as well as evidence that FDA does not cite indicates that dual users, even if they reduce cigarette consumption, have increased health risks. Reduced cigarette consumption does not ensure health benefits.

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[60] Wills TA, Soneji SS, Choi K, Jaspers I, Tam EK. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J. 2021 Jan 21;57(1):1901815. doi: 10.1183/13993003.01815-2019. PMID: 33154031; PMCID: PMC7817920. Available: https://pubmed.ncbi.nlm.nih.gov/33154031/

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[62] Omar El-Shahawy, Tanmik Shah, Olufunmilayo H. Obisesan, Meghan Durr, Andrew C. Stokes, Iftekhar Uddin, Ria Pinjani, Emelia J. Benjamin, Mohammadhassan Mirbolouk, Albert D. Osei, Tom Loney, Scott E. Sherman, Michael J. Blaha. Association of E-Cigarettes With Erectile Dysfunction: The Population Assessment of Tobacco and Health Study. American Journal of Preventive Medicine 2021, ISSN 0749-3797, https://doi.org/10.1016/j.amepre.2021.08.004. Available: https://www.sciencedirect.com/science/article/pii/S0749379721004293

[63] Wills TA, Soneji SS, Choi K, Jaspers I, Tam EK. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J. 2021 Jan 21;57(1):1901815. doi: 10.1183/13993003.01815-2019. PMID: 33154031; PMCID: PMC7817920. Available: https://pubmed.ncbi.nlm.nih.gov/33154031/

The risks of dual use are particularly important because, according to RJR (as quoted by FDA on TPL page 14), similar numbers of smokers intended to become dual users as to switch (quit smoking): "Most respondents indicated that their intended behavioral change with the new products was to switch to the product (38.5-52.8%) or to dual use (combusted cigarettes and the new products, 39.7-52.8%) with the intention of using fewer combusted cigarettes."

Like its failure to provide quantitative estimates of the claimed general cessation benefit of e-cigarettes, FDA failed to quantify the effects of dual use even with reduced cigarette consumption. In both cases, it is likely that there are no such benefits to offset the risks to youth.

FDA considers e-cigarettes having high addictive potential a good thing

FDA is allowing a high level of nicotine in Vuse Solo because "if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using" (TPL page 11). The level of nicotine that FDA is permitting is three times the nicotine concentration that is legally permitted in Canada, the UK and Europe.[64]

The FDA recognizes that, "The nicotine levels ***may pose an addiction risk for non-tobacco users*****,"** but then goes on to assert that "the risk is no higher than other currently available tobacco products due to relatively low abuse liability of the new [Vuse Solo] products." But the FDA does not present or cite any actual data on abuse liability of Vuse Solo or e-cigarettes generally for youth or other non-users.

The whole argument is based on RJR's comparison of Vuse with one of their minor brands, Newport Gold, which does not appear on a list of the top 100 brands.[65] (Newport Menthol Gold King ranked number 70 and Newport Menthol Gold 100 ranked 95. For comparison Newport Menthol Green 100 and Newport Menthol Green King ranked third and fourth.) This leaves open the question of whether RJR was gaming the system by selecting this brand as the comparator.

Moreover, the FDA does not address the issue that abuse liability for youth may have a different dynamic than among adult current tobacco users.

The Vuse Solo marketing order sets a dangerous precedent for other e-cigarettes

As noted earlier, FDA's pattern of making favorable assumptions on RJR's behalf sets a dangerous precedent for other e-cigarettes. Based on FDA's TPL for Vuse, it will be difficult to deny marketing orders for Juul or any other non-flavored (except menthol) closed system e-cigarette.

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[64] Myers ML. FDA's Authorization of High-Nicotine Vuse E-Cigarette Leaves Kids at Risk of Addiction (Statement of Matthew L. Myers, President, Campaign for Tobacco-Free Kids). October 12, 2021. (press release) Available: https://www.tobaccofreekids.org/press-releases/2021_10_12_vuse-fda-high-nicotine

[65] Carmines E, Gillman IG. Comparison of the Yield of Very Low Nicotine Content Cigarettes to the Top 100 United States Brand Styles. Beiträge zur Tabakforschung International/Contributions to Tobacco Research. 2019; 28(6); 253-266. https://doi.org/10.2478/cttr-2019-0005. Available: https://www.sciendo.com/article/10.2478/cttr-2019-0005

FDA has reversed other decisions when errors were brought to its attention

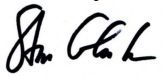
For comparison, the Vuse Solo marketing granted orders were issued within days of FDA informing Turning Point Brands (a manufacturer of e-liquids and other ENDS products) that it had rescinded its September 14 Marketing Denial Order (MDO) for some of its flavored e-liquids because, "Upon further review of the administrative record, FDA found relevant information that was not adequately assessed."[66] FDA similarly rescinded its MDOs for at least two other flavored e-liquid products (Fumizer[67] and Humble Juice Co.[68]) shortly thereafter. (Mr. Zeller was reported to say that FDA is being sued for 46 MDOs,[69] including the more than 30 companies named on this list of companies challenging MDOs.[70]) In rescinding these MDOs, FDA properly acknowledged that it erred in reaching these marketing decisions and took appropriate remedial actions.

FDA is r*equired*[71] to issue an order withdrawing a marketing granted order if it finds that the marketing of the product is no longer appropriate for the protection of the public health or if the PMTA application contained or was accompanied by an untrue statement of a material fact. Indeed, FDA stated in the Vuse Solo Marketing Granted Order,[72] "The products subject to these marketing granted orders are subject to withdrawal or temporary suspension as described in section 910(d) of the FD&C Act."

As described in detail above, FDA made significant errors in analyzing the evidence that the TPL suggests was presented in the Vuse PMTAs and did not correctly consider the current scientific literature. ***We urge FDA to acknowledge these errors as it did in the case of the rescinded MDOs and withdraw the marketing granted orders for Vuse Solo.***

In addition, analyses of pending PMTA applications for other e-cigarette products should be carefully assessed to avoid the problems with the Vuse Solo marketing order before they are finalized.

Sincerely,



Stanton A. Glantz, PhD

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[66] Turning Point Brands, FDA Rescinds Previously Disclosed Marketing Denial Order for Turning Point Brands' Vapor Products, October 11, 2021. Available: https://www.turningpointbrands.com/investor-relations/news/news-details/2021/FDA-Rescinds-Previously-Disclosed-Marketing-Denial-Order-for-Turning-Point-Brands-Vapor-Products/default.aspx

[67] Tobacco Reporter, FDA Rescinds Another Marketing Denial Order, October 26, 2021. Available: https://tobaccoreporter.com/2021/10/26/fda-rescinds-another-marketing-denial-order/

[68] PR Newswire, FDA Rescinds Marketing Denial Order for Humble's Flavored E-Liquids, November 5, 2021. Available: https://www.prnewswire.com/news-releases/fda-rescinds-marketing-denial-order-for-humbles-flavored-e-liquids-301417816.html

[69] Convenience Store News, FDA Denies PMTAs for 200,000 Products to Date; The Agency is Currently Being Sued for 46 of the Refusals, October 29, 2021. Available: https://www.csnews.com/fda-denies-pmtas-200000-products-date#:~:text=The%20agency%20is%20currently%20being,sold%20in%20the%20United%20States.

[70] Vaping 360, Jim McDonald, Vape Company Challenges to FDA Denial Orders, updated November 5, 2021. Available: https://vaping360.com/vape-news/111563/vape-companies-challenging-fda-marketing-denials/#

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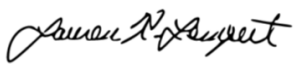

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