FDA bent over backwards to authorize sale of RJR's Vuse Solo e-cig

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November 8 2021

On October 12, 2021, FDA authorized the sale of RJ Reynolds' Vuse Solo e-cigarette.

When I read the FDA's Technical Project Lead summary of its scientific justification for authorizing the sale of RJ Reynolds' Vuse Solo e-cigarette, I was struck by the fact that it ignored the broad scientific literature on e-cigarettes and seemed to accept industry-framed arguments.

In particular:

- 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 shocking statement, "Overall, the available evidence to date does not adequately address whether new product use in youth and young adults leads to regular smoking."
- 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 as consumer products do not help smokers quit and that they promote relapse in former smokers.
- 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 and 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 and fails to adequately address dual use.
- FDA considers e-cigarettes having high addictive potential a good thing.

Just two facts seriously question FDA's decision to authorize continued marketing of e-cigarettes as "appropriate for the protection of public health," the legal standard: (1) millions of youth are attracted to e-cigarettes, and (2) there is no population benefit of e-cigarettes as consumer

products use on smoking cessation. 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.

In the press release announcing its decision, FDA Center for Tobacco Products Director Mitch Zeller said, "Today's authorizations are an important step toward ensuring all new tobacco products undergo the FDA's robust, scientific premarket evaluation. The manufacturer's data demonstrates its tobacco-flavored products could benefit addicted adult smokers who switch to these products – either completely or with a significant reduction in cigarette consumption – by reducing their exposure to harmful chemicals."

But a careful read of FDA's Technical Project Lead report (TPL) reveals that it is filled with incomplete and contradictory information that reflects a consistent willingness to give RJR the benefit of the doubt.

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.

Hopefully FDA will take the problems identified in this post to heart and be more rigorous in assessing the remaining PMTA applications. Absent specific reliable evidence that shows that a proposed product will behave very differently from e-cigarettes in general, FDA should deny the remaining PMTAs.

FDA should also reassess Vuse Solo in light of the full scientific literature and withdraw its flawed marketing order.

NOTE: This post addresses the scientific problems with the Vuse Solo marketing order; it does not address problems with the weak marketing restrictions.

This commentary is available as a PDF.

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

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

FDA's summary of the logic behind their decision (known as the Technical Project Lead report, or 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%).[40]" As noted above, by 2021, 10.5% of kids and 10.8% of high school students were using Vuse, a 50% increase over 2020. 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*." The TPL assumes that the increase in Vuse brand popularity does not apply to Vuse Solo or flavors. This is one of many examples of FDA ***giving RJR the benefit of the doubt.*** In fact, the FDA has brand-specific data on flavors from the NYTS, but did not use that information in its TPL or yet release the data to the scientific community or the public.

Most important, FDA was willing to trade off addicting new youth to Vuse to help current cigarette smokers reduce their risk. ***But FDA never estimates how many youth the FDA is willing to sacrifice, including the immediate adverse health effects on youth, or how many adult smokers who benefit and by how much, the central question of the tradeoff FDA made.***

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

Perhaps the most shocking and uninformed statement the FDA makes is that "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 risk of cigarette smoking. Once they start, kids have 3-6 times the odds of going on to add cigarettes to e-cigarette use (meta-analysis 1, meta-analysis 2) with the newer studies showing 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 eventually becoming a daily cigarette smoker. The FDA also ignored an 2020 meta-analysis that showed that youth ever e-cigarette use more than doubled the odds of later current smoking (OR 2.21, 95% CI 1.72-2.84; Figure S2).

A more recent meta-analysis of all available longitudinal studies (Figure 1) found similar results.

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. 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.

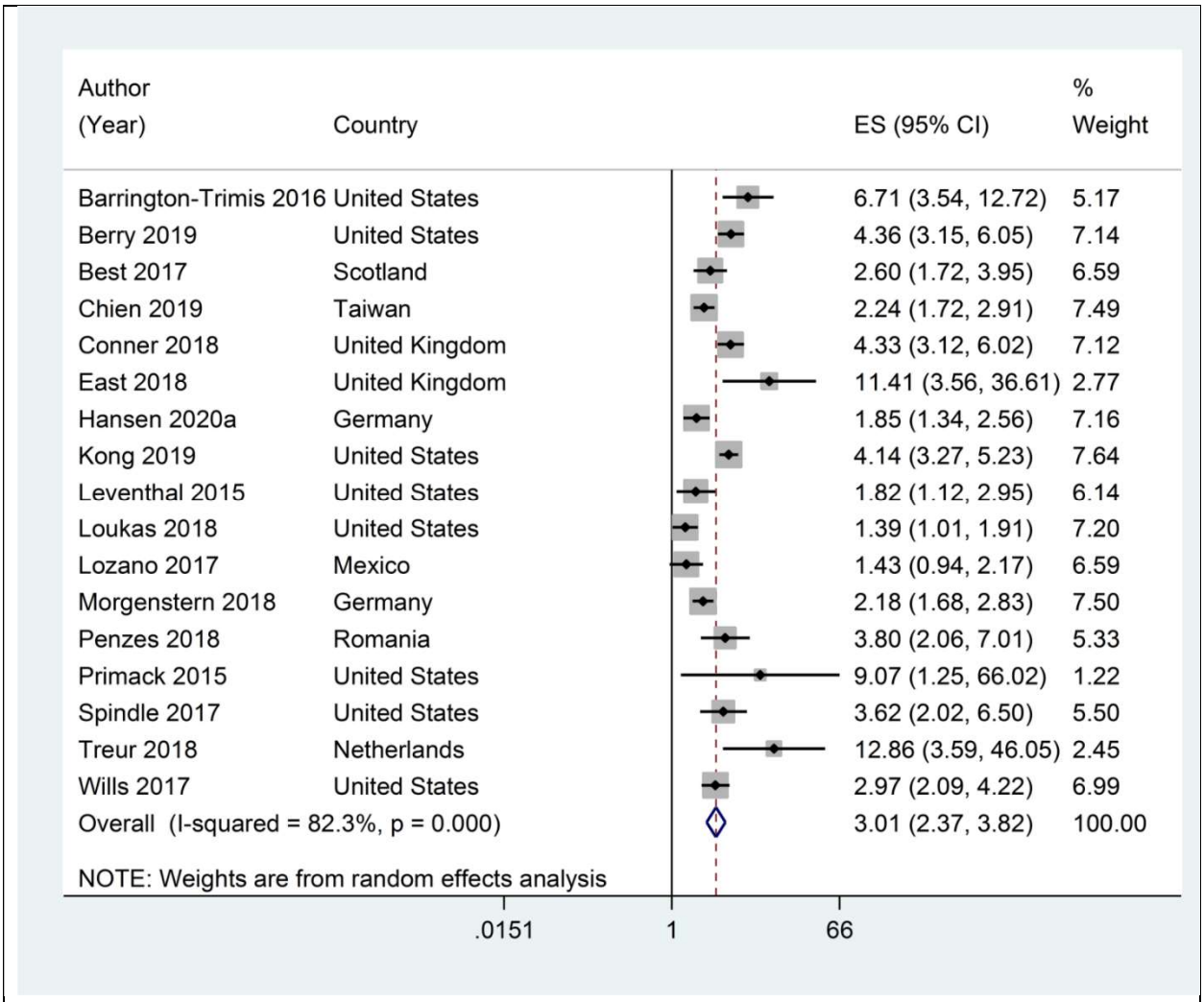

Figure 1. All the longitudinal studies show that among youth who had never smoked a cigarette at baseline, e-cigarette use elevated the relative risk of smoking at followup. Combining all the studies the adjusted risk ratios for cigarette smoking was about tripled (ever smoking: OR 3.01, 95% CI: 2.37 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

E-cigarettes are expanding the youth tobacco epidemic

The FDA ignored the very strong and consistent evidence that e-cigarettes are expanding the tobacco epidemic by ***attracting large numbers of youth at low risk of initiating nicotine use with cigarettes.***

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).

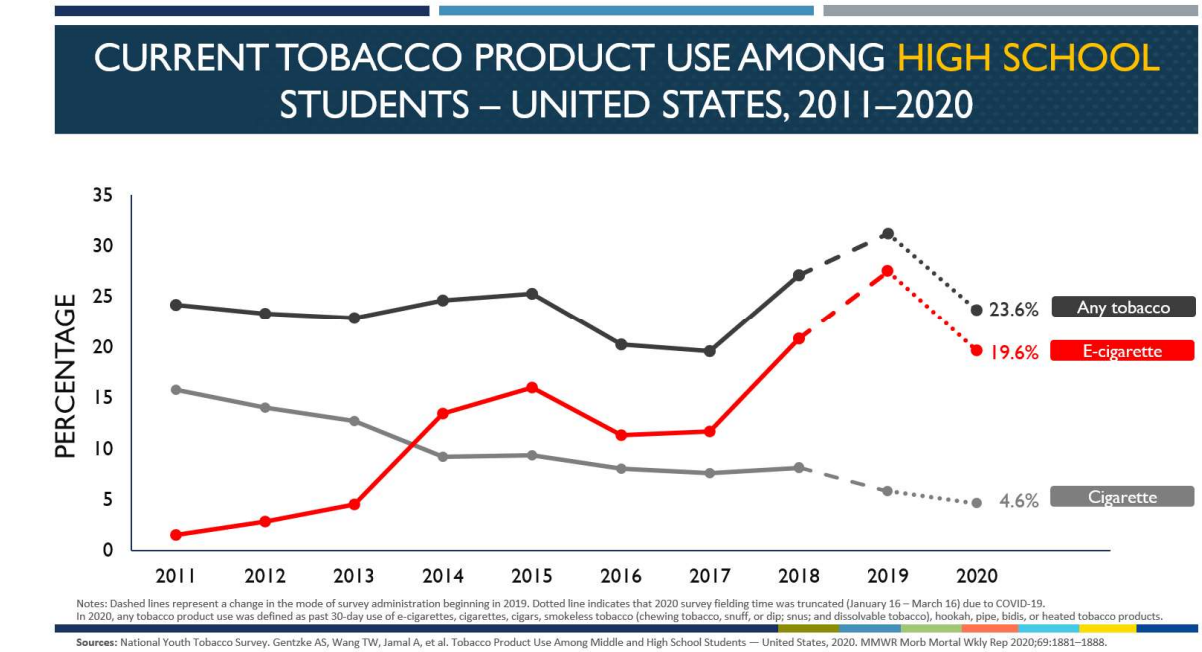

Figure 2. E-cigarette use and total tobacco use have dramatically increases among high school seniors, with e-cigarette increasing much more and faster than cigarette use declined. Source: CDC.

Consistent with these findings, the upswing in youth e-cigarette use was also associated with a slowing in the decline of current cigarette smoking.

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

For example, the FDA 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 is based on an assumption that could prove invalid, particularly if FDA allows menthol Vuse and other e-cigarettes (as I expect they will). Several studies provide direct evidence that if menthol flavor remains available, youth will simply shift from other flavors to menthol.

A national study using Neilsen 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 found similar results: Use of the restricted flavors dropped, while mint pod use increased. Tobacco and menthol pod use remained stable.

Another study 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.

The fact that FDA explicitly did not act on the Vuse menthol PMTA and that it has granted marketing orders for Philip Morris' menthol IQOS product and four US Tobacco menthol smokeless products raises serious concerns that menthol e-cigarettes will be authorized. Based on history it is likely that RJR (and other companies) can replace other flavors with menthol through effective marketing.

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 meta-analysis we published last year (not cited by the FDA) based on 55 population observational studies as well as a newly published one 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 meta-analysis 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. (Our meta-analysis considered both cohort and cross-sectional studies; analyzing them separately showed no significant difference in the results.)

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

Despite these facts and incomplete information in the RJR PMTA application for Vuse, (as reported by FDA; the PMTA is not made publicly available) FDA nevertheless concluded that Vuse 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 is based on the assumption that smokers would "switch completely."

In addition, rather than relying on specific evidence that, unlike e-cigarettes in general, Vuse Solo had a specific cessation benefit, the FDA fell back on the 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 simply concluded "This study suggests that e-cigarette use patterns are highly variable over a 1-year period."
- Reference 28 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."
- Reference 29 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 (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 …" (Wang et al, 2020)
- "We did not find quality evidence for an association between e-cigarette use and smoking cessation." (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." (Barufaldi et al, 2021)

Figure 3. E-cigarette use and subsequent smoking cessation in cohort studies, adjusted analyses

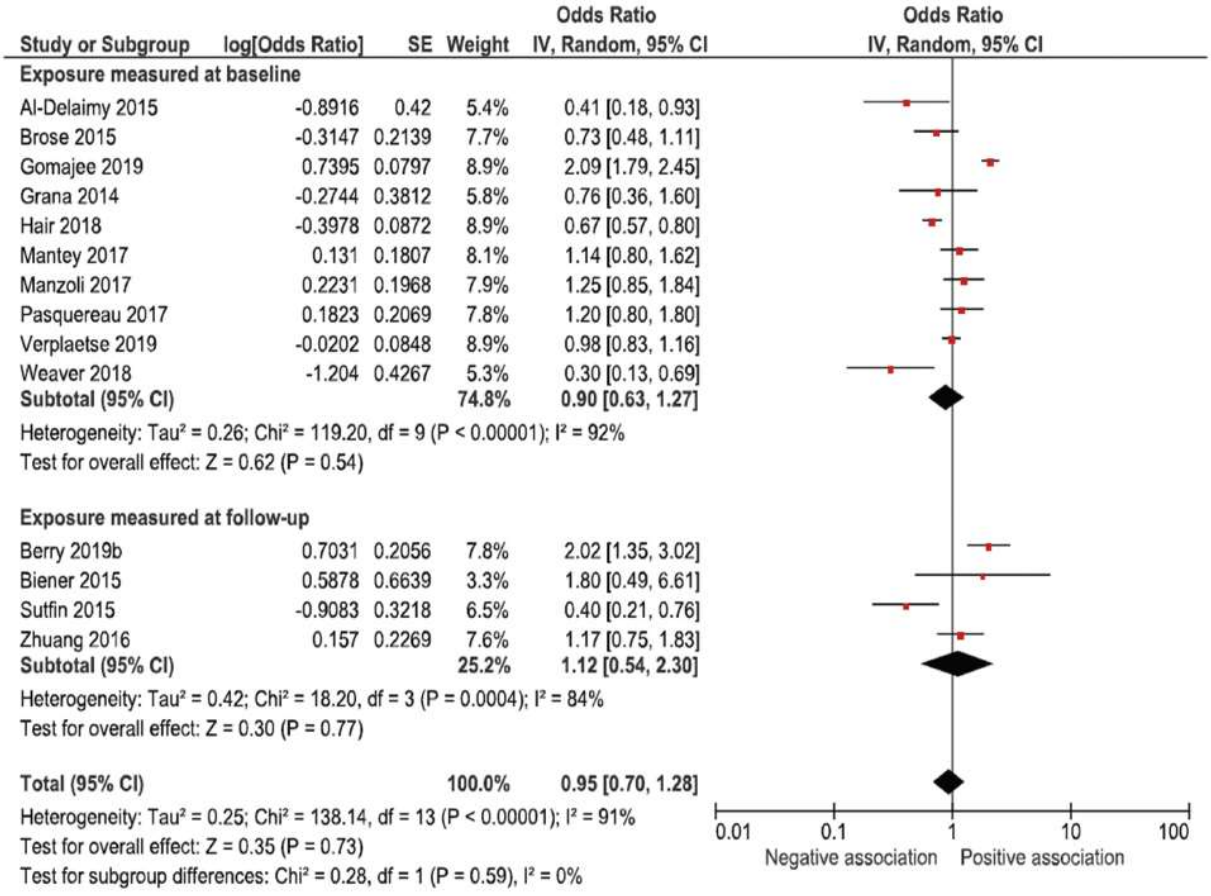

Figure 3. E-cigarette use has no detectable effect on smoking cessation in cohort (longitudinal) studies. The overall odds ratio for quitting is 0.95 (95% CI 0.70-1.28; p=0.73), which is indistinguishable from 1.0 (no effect). Among all the studies in this meta-analysis only 2 showed significant increases 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 with inventing the modern e-cigarette in 2003 as a smoking cessation device was still smoking in 2021. Even he did not "switch completely."

(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 but chose not to take it to market.)

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'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 HPHC (Harmful and Potentially Harmful Constituents) 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 a well-justified expanded HPHC list that addresses this problem, although they never finalized it.

Propylene glycol ("PG") and glycerol (also known as glycerin, vegetable glycerin, or "VG") are ingredients found in Vuse that FDA considered to be harmful constituents on the updated list, Yet FDA did not comment on the risks associated with these constituents in the Vuse 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 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 beyond cancer risk

Moving beyond this limited consideration is particularly important in light of the fact that e-cigarettes deliver thousands of toxins with a risk profile *different* from cigarettes. The toxic load e-cigarette impose is not simply a subset of cigarette toxins.

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

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

> 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 cancinogenesis, 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.***
>
> ***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. <<PP>>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]

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, 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 had also lower levels of biomarkers.[52] ***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***.

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]

Specifically, reference 53 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 reference 61 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 (reference 62) finds that there is ***no overall health benefit of cigarette reduction in cigarettes per day*** benefits:

> 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 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 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 also show increased risks of dual use (Alzahrani et al, 2018**,** Osei et al, 2019).

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, they ignore the longitudinal studieshttps://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.

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 as legally permitted in Canada, the UK and Europe.

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. (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, I do not see how they can deny marketing orders for Juul or any other non-flavored (except menthol) closed system e-cigarette.

Hopefully FDA will take the problems identified in this post to heart and be more rigorous in assessing the remaining PMTA applications. Absent specific reliable evidence that shows that a proposed product will behave very differently from e-cigarettes in general, FDA should deny the remaining PMTAs.

FDA should also reassess Vuse Solo in light of the full scientific literature and withdraw its flawed marketing order.