Toward Developing Minimum Standards to Ensure that FDA Permissive PMTA Orders for E-Cigarettes Are "Appropriate for the Protection of the Public Health" and "Not Arbitrary or Capricious" (and Ethically Defensible)

Background

All e-cigarettes currently on the market do not have permissive PMTA orders and, consequently, are illegal. Many remain on the market without being enforced against because of FDA's announced enforcement discretion of allowing all e-cigarettes deemed under FDA's tobacco control jurisdiction in August 2016 to stay on the market without the legally required PMTA orders so long as applications to secure one are filed by August 2022. FDA has already taken steps toward revising that enforcement discretion policy, proposing to move that date up to August 2021 for most e-cigarettes and to begin enforcement against flavored e-cigarettes (other than tobacco, menthol, or mint) unless sold only in adult-only areas. More recently, a U.S. District Court ruled that FDA's enforcement-discretion policy of waiting until 2022 is not legally permitted. What exactly will happen regarding PMTA's and the e-cigarettes currently on the market is still uncertain, but it is clear that some e-cigarettes will be applying for permissive PMTA orders well before August 2022 and perhaps quite soon.

FDA may not issue a PMTA order to allow an e-cigarette to enter or stay on the U.S. market unless FDA determines that allowing it on the market pursuant to the permissive order is "appropriate for the protection of the public health." While that standard has not been fully defined or firmly established, it generally requires FDA to reasonably determine that:

(1) The applicant e-cigarette is less harmful to users and/or exposed non-users than smoking cigarettes or other smoked tobacco products currently on the market; *and*

(2) The impact of the e-cigarette's marketing (subject to applicable laws and regulations and to any additional restrictions and requirements in the permissive order) on e-cigarette and smoking initiation, cessation, switching, dual use, relapse, consumption levels, and non-user exposure would likely produce a net public health gain by producing more new health gains than new health losses; *and*

(3) There is either:

   (a) No risk that the e-cigarette's marketing might produce a significant net public health loss, instead; or

   (b) The likelihood and size of any possible net public health loss caused by the e-cigarette's marketing would, at worst, be so much smaller than the likelihood and size of the potential net public health gains that running the net-loss risk would still be "appropriate for the protection of the public health."[1]

Making these determinations, however, is complicated by the remaining uncertainties about the relative harmfulness to a smoker or brand-new initiate using any specific e-cigarette compared to smoking, dual

[1] For more detail, please see the previously circulated memo on the standards applicable to FDA tobacco control rulemaking and tobacco control orders. That memo and all the other pre-meeting background memos are available on the project meeting website.

use or multiple-product use, or no use at all, and by the inevitable difficulties in reliably predicting the many different possible near-term and longer-term impacts on consumer behavior from allowing an e-cigarette on the market, especially given the many other unpredictable variables at play (e.g., industry marketing, lobbying, and litigation practices; other industry and market changes; and changes to federal, state, and local regulatory policies).

Because of these inherent uncertainties and difficulties – and the manufacturers' strong profit motive to maximize use, regardless of public health impacts – ruling out any risk that a permissive PMTA order might produce a net public health harm could be impossible.

For these same reasons, it will likely also be very difficult, if not impossible, for FDA to estimate with any precision or certainty the relative likelihood and size of the potential net public health gains and the possible net public health harms from allowing an applicant e-cigarette to enter or stay on the market. And the larger that imprecision and uncertainty is, the more difficult it would be for FDA to determine that the likelihood and size of any possible net public health loss caused by the e-cigarette's marketing would, at worst, be so much smaller than the likelihood and size of the potential net public health gains that running the net-loss risk would be "appropriate for the protection of the public health."

But FDA could reduce the size and scope of that underlying imprecision and uncertainty and improve the accuracy and reliability of its "appropriate" determinations by:

1. Requiring applicants to show that they have taken advantage of all reasonably available measures to make their applicant e-cigarettes less harmful without interfering with their operation or with their ability to serve as effective smoking substitutes and secure net public health gains.
2. Including in its permissive orders any readily available restrictions or requirements on the packaging, labeling, marketing, or sale of the applicant e-cigarettes that could reduce the likelihood or size of any new health harms that might be caused by the e-cigarettes or their marketing without reducing the likelihood or size of the expected net public health gains.

Following such an approach would not enable FDA to eliminate the risk that a permissive order might end up producing new public health harms, or even precisely quantify the likelihood and size of the potential net public health gain versus possible net public health loss. But this approach would reduce the likelihood and size of the still-not-possible-to eliminate net public health risks, and it would increase the still-not-reliably-quantifiable ratio between the likelihood and size of the possible net public health harms and the likelihood and size of the potential net public health gains. Following this approach would also help ensure that the permissive order would be working to secure net public health gains with smaller amounts of underlying new health harms.[2]

[2] For example, allowing an e-cigarette on the market in ways that would reduce the number of quality-adjusted life years lost to tobacco-nicotine use by an estimated 10,000 through increasing the QALYs among smokers who switched by 15,000 and reducing the QALYs among other users by 5,000 would be much less desirable, from a public health or ethical perspective, than securing that same 10,000 reduction in lost QALYs by increasing the QALYs among the switching smokers by 10,000 and not reducing the QALYs among any other users at all.

Along the same lines, it appears that FDA could have a legal duty under the Tobacco Control Act and the APA's "not arbitrary or capricious" standard to take advantage of any readily available measures to reduce the likelihood and size of any new individual or public health harms that might be produced by issuing a permissive PMTA order that would not also reduce the likelihood and size of the expected net public health gains.[3]

Similarly, FDA can also be seen as having an ethical duty to structure its permissive PMTA orders to reduce the likelihood and size of any new individual or public health harms that might be produced by allowing the e-cigarette to enter or stay on the market -- at least to the extent that those health risks could be reduced without reducing the likelihood and size of the expected net public health gains or when the reductions in new health harms caused by the permissive order would be disproportionately larger than any related reduction to the likely gross or net public health gains.

[ANY QUESTIONS OR CONCERNS ABOUT THE ABOVE INFORMATION AND ANALYSIS?]

Process

Following the above analysis, this project will evaluate different possible requirements and restrictions FDA could place on e-cigarettes submitting PMTAs and receiving permissive orders in terms of:

A. Would the proposed requirement or restriction placed on the PMTA e-cigarette most likely make using the e-cigarette less harmful and risky – thereby increasing the potential health gains of those using the e-cigarette in harm-reducing ways and reducing the health harms and risks of those using the e-cigarettes in harmful ways? and/or

B. Would the proposed requirement or restriction most likely reduce the number of people using e-cigarettes in harmful ways more than it would reduce the number of people using the e-cigarette in harm-reducing ways? [Or, if not, could it be revised to do so?]

C. Does the proposed restriction or requirement clearly make sense from a purely public health perspective – or could it be revised to do so?

D. Are there any ethical concerns regarding the restriction or requirement and, if so, are there any ways to address them without risking the public health gains?

For considering these possible e-cigarette PMTA requirements and restrictions, the project assumes that:

- The application would be pending under existing regulatory and marketing conditions, with the market consisting of all tobacco-nicotine products on the market today, as well as IQOS (which FDA just recently allowed) – but with all e-cigs currently on the market ultimately having to comply with any restrictions and requirements placed on the hypothetical PMTA-applicant e-cigarette being considered here (perhaps sooner rather than later).
- The applicant e-cigarette (and all other e-cigarettes allowed to enter or stay on the market) would be required to comply with all existing laws and regulations that apply to e-cigarettes.

[3] See the previously circulated memo on the standards applicable to FDA tobacco control rulemaking and tobacco control orders.

- FDA would place the same restrictions on Internet/electronic sales or advertising of the e-cigarettes that it placed on IQOS via its permissive PMTA order (requiring strong age-verification prior to ad exposure or sales).
- There would be rigorous post-market surveillance so that the e-cigarette could be pulled from the market or the requirements and restrictions in its permissive order revised if its availability and marketing were creating more public health harms than benefits. But preventing any such public harms in the first place (without disproportionately reducing public health benefits) is considered preferable.

[ANY QUESTIONS OR CONCERNS ABOUT THIS PROCESS?]

Possible PMTA Requirements and Restrictions FDA Could Apply

I. ***Make the e-cigarettes less harmful.*** Require PMTA applicants to show they have taken all technically achievable steps to make the e-cigarettes as minimally harmful as possible that would not interfere with its ability to deliver nicotine effectively to consumers or make it significantly less attractive to adult smokers as a smoking substitute. Including:

A. Designed and manufactured reliably to prevent explosions or burns.

B. Designed to prevent higher temperatures than required to deliver nicotine effectively (which can create more toxins).

C. Minimal contamination.

D. No additives (i.e., ingredients, such as added flavors, not necessary for the product to function as an e-cigarette) that either are harmful or potentially harmful substances or create harmful or potentially harmful constituents (HPHCs) when heated and inhaled via the e-cigarette.[4]

E. No ingredients necessary for the e-cigarettes operation that are significantly more harmful or potentially harmful than other substitute ingredients that would work just as well.[5]

F. [Any other ways to make the e-cigarette, itself, less harmful that should be considered?]

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[4] Nicotine and other ingredients needed to enable the e-cigarette to deliver nicotine to users effectively in an inhalable form (like cigarettes do) would qualify as necessary ingredients not subject to this restriction. An underlying assumption here is that this restriction would not prohibit all added flavors. If it would, an exception could be made for those added flavors considered to be the least harmful or potentially harmful compared to other added flavors.

[5] For example, there is evidence that using vegetable glycerin instead of propylene glycol in the e-cigarette liquid might produce greater health harms/risks. Son, Y, et al., "Hydroxyl Radicals in E-Cigarette Vapor and E-Vapor Oxidative Potentials under Different Vaping Patterns," *Chem. Res. Toxicology* (Epub. April 23, 2019). But it is also possible that using both vegetable glycerin and propylene glycol produces a more cigarette-like throat hit, enabling the e-cig to serve more effectively as a smoking substitute. Harvanko, A, "Stimulus effects of propylene glycol and vegetable glycerin in electronic cigarette liquids," *Drug Alcohol Dependence* 194: 326-29 (Jan. 1, 2019).

II. ***Allow e-cigarettes on the market only as less-harmful alternative products for smokers (and for former-smokers who have already switched)*** – because there is no other use that produces health gains or is not harmful or risky. Limiting the e-cigarette's permitted sale and use to smokers and former smokers who have already switched would also sharply curtail the manufacturers' and sellers' related 1'st Amendment commercial speech protections (which apply only to seller communications to a product's legal consumers). This restriction could be operationalized by:

A. Permitting sales only to verified adults who self-identify themselves to the sellers as smokers or as former smokers now using e-cigarettes or other alternative tobacco-nicotine products (could be verbal or by signing form or checking box on sheet or screen).[6]

B. Requiring the warnings on and in all e-cigarette packages, discussed below.

III. ***Require special additional warnings and instructions for use***, including:

A. Require something like the following text on all e-cigarette packages:

"WARNING: This Product is Harmful and Addictive. FOR USE ONLY AS A SMOKING SUBSTITUTE. Any other use will increase health harms and risks."

- At least the same size, etc. as the warning labels TCA requires for smokeless tobacco products (e.g., 30% of two principal display panels of package).
- On fluorescent yellow background to increase visibility.[7]

B. More detailed product inserts stating that the e-cigarette is for use only as a smoking substitute and including information about harms and risks from using the e-cigarette; how to secure health gains by using as the e-cigarette as a smoking substitute; how even larger health gains can be secured by quitting all tobacco-nicotine use; harms and risks from dual use (unless moving toward complete substitution or total quitting); how to use the e-cigarette in ways that minimize harms and risks to self and others; how any use except by smokers as smoking substitute is harmful; etc.[8]

C. [Any other packaging and labeling characteristics to support constructive use and discourage harmful use?]

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[6] Although easily evaded by adults willing to lie, this requirement would still emphasize that e-cigs are only for use as a cigarette substitute for adult smokers and former smokers, would impede some sales to non-smokers and non-adults, and would be much simpler and easier to implement than any less permeable system. It would also help to establish that only adult smokers and former smokers are the product's legal customers for 1st Amendment purposes.

[7] Lempert, LK & Glantz, SA, "Implications of tobacco industry research on packaging colors for designing health warning labels," *Nicotine & Tobacco Research* (May 4, 2016).

[8] The text and format of the warning label and the product inserts would be based on available research regarding which messaging and formats would likely worked most effectively to move smokers who would not otherwise quit to try and regularly use the e-cigarettes, instead, and which worked most effectively to prevent harm-increasing uses of the e-cigarettes by smokers and nonsmokers.

IV. ***Restrict the e-cigarette's advertising and other marketing to messaging designed to reach only adult smokers with minimum exposure among youth and nonsmokers.***[9]

A. No retail product displays or publicly visible ads except at adult-access-only retail outlets that sell tobacco products or e-cigarettes.

B. At youth-accessible retail outlets: No product displays or visible ads. But signage allowed with text that identifies product by name and type, lists price, and states that additional information about the product is available on request to adult smokers and former-smoker e-cigarette users who request it.

C. Other advertising allowed only through direct communications (direct mail, email, social media) to pre-verified adults who self-identify as current smokers or former smokers who have switched to using e-cigarettes.

[No new restrictions on these permitted communications, except they must include the above-described warning, not be false or misleading, and must otherwise comply with TCA and rules.]

D. [Other possible advertising restrictions to list and discuss?]

V. ***Restrict flavors by allowing only menthol, mint, and tobacco flavors (to parallel cigarette flavors) and any other flavors research shows will prompt more constructive switching from smoking than new initiation by youth who otherwise would use no tobacco-nicotine products***.[10]

VI. ***Restrict the e-cigarette sales to adult-only sales outlets or areas***.

VII. [Any other possible PMTA restrictions or requirements to list and discuss?]

Related Possible PMTA Process Recommendations:

VIII. FDA should adopt and publicize a policy of rejecting, as not "appropriate for the protection of the public health," any PMTA applications from e-cigarettes that are clearly more harmful to users than any e-cigarettes that have already received permissive PMTA orders and are readily available to

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[9] Messaging designed to reach adult smokers (e.g., the just-described warnings and inserts for cigarette packs and other smoked-tobacco-product packaging and the advertising described here) would reach both smokers who would benefit from switching to e-cigarettes (would not otherwise quit) and those who would not (would otherwise quit all use). In any given year, however, close to 70% of all smokers say they are interested in quitting, but only about 50% actually try to do so, and only about six percent successfully quit for at least six months. Stephen Babb et al., "Quitting Smoking Among Adults—United States, 2000–2015," *MMWR* 52: 1457 (2017). That means that the smoker-directed warnings with switching information and the permitted smoker-directed e-cigarette ads would reach roughly five smokers not otherwise interested in quitting and more than 10 smokers trying or intending to quit who would otherwise fail (and could, therefore, benefit from receiving encouragement to use e-cigs) for every single adult smoker it reached who would otherwise quit successfully (for at least six months) and could be harmed by using e-cigarettes, instead.

[10] As noted above, all HPHC added flavors would also be prohibited.

smokers – unless the applicant establishes that the specific characteristics which make the applicant e-cigarette more harmful will also enable its availability and marketing to increase overall smoker switching to e-cigarettes and produce larger related overall public health gains.[11]

IX. If FDA allows an e-cigarette on the market with a permissive PMTA order that includes specific restrictions and requirements on the product or its packaging, labeling, marketing, or sale that FDA has determined are necessary to make issuing a permissive PMTA order more certainly "appropriate for the protection of the public health" or otherwise more effective for protecting and promoting the public health, FDA should concurrently announce that after 90 (120?) days, FDA will exercise its discretion to focus its PMTA-related enforcement efforts toward removing any e-cigarettes still on the market without permissive PMTA orders that FDA finds are not in compliance with those same restrictions and requirements.[12]

X. When FDA issues a new permissive PMTA order for an e-cigarette, the agency should reevaluate any previously issued permissive PMTA orders for e-cigarettes (or for other PMTA products, such as IQOS, that allow nicotine to be inhaled) to see if they need to be revised or rescinded because allowing the previously permitted PMTA products to stay on the market as ordered is no longer "appropriate for the protection of the public health," given the ready availability of the newly permitted e-cigarette.[13]

XI. [Any other procedural PMTA recommendations to list and discuss?]

[THANKS FOR READING!]

[Please let Eric Lindblom know if you have any major questions or concerns, especially about the Background of Process sections, or if you have any suggestions for additional PMTA restrictions or requirements the project should consider.]

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[11] If a newly allowed e-cigarette were significantly more harmful than other e-cigarettes already on the market with permissive PMTAs, it would increase health harms if smokers switched to the new e-cigarette instead of to already available less-harmful e-cigarettes or if users of the less-harmful e-cigarettes switched to using the new more-harmful e-cigarette.

[12] Such an enforcement policy would dramatically increase and accelerate the potential harm reductions from FDA issuing a permissive PMTA order for any e-cigarette. If announced ahead of time, it would also provide a powerful incentive for manufacturers to seek permissive PMTA orders (none have yet done so), as obtaining a permissive order would not subject the PMTA-order e-cigarette to restrictions and requirements that other e-cigarettes on the market would not have to comply with immediately, as well, and the new enforcement policy would likely shrink the number of e-cigarettes the new PMTA-order e-cigarette would have to compete against.

[13] This policy would further increase the incentives for manufacturers to obtain PMTA orders for their e-cigarettes and, more specifically, spur technological innovation to make the new applicant e-cigarettes less-harmful and more effective as smoker substitutes (and less likely to increase health-harming use) than e-cigarettes already on the market with PMTAs, thereby increasing the likelihood that e-cigarettes already on the market with permissive PMTA orders would have their orders rescinded.