Tobacco Product Standard for Nicotine Level:

Protecting Against Unintended Consequences by Expanding the Scope of the Rule to All Inhaled Recreational Nicotine Products

Docket No. FDA-2017-N-6189

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This comment details how the proposed product standard can create unintended public health harm if the standard is written in a way that can be used by the tobacco industry to simply shift the mix of dangerous products that it markets to continue to build its markets. Specifically, if the nicotine product standard for cigarettes or even all combustible tobacco products is not implemented in the broader context of the entire recreational nicotine market, the product standard could create substantial public health risks. ***FDA must develop the standard in a way that explicitly considers that: 1) e-cigarettes and other non-combusted nicotine products do carry health risks, and 2) FDA resources must be devoted to targeted public education campaigns and concurrent regulatory action to ensure that the combustible product standard does not inadvertently increase nicotine use among youth and young adults.***

3. POSSIBLE COUNTERVAILING EFFECTS

(1) In addition to a nicotine tobacco product standard, should FDA consider any additional regulatory action to address the possibility of migration to, or dual use with, other tobacco products?

Implicit in the framing of this Advanced Notice of Proposed Rule Making (ANPRM) is the assumption that, aside from its addictive properties, nicotine has few direct adverse health effects. Another assumption implicit in the ANPRM is that creating a product standard to reduce nicotine to non-addictive levels would move smokers to purportedly less harmful forms of nicotine delivery and would result in lower harm both to individual smokers and to the population as a whole. However, if the nicotine concentration in cigarettes is reduced, it is likely that a significant fraction of cigarette smokers will use e-cigarettes or other new products to supplement their nicotine consumption. Rapidly accumulating evidence from the study of e-cigarettes as well independent analysis of the Philip Morris International Modified Risk Tobacco

Product application for its IQOS heated tobacco product[1] calls both these assumptions into question.

Pulmonary Effects of Nicotine

It is generally assumed that the negative health effects of cigarettes are due to the many chemical species produced by combustion and not due to nicotine itself. However, recent experimental evidence suggests nicotine may significantly contribute to the pulmonary toxicity

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[1] FDA. Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications. Available at https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm546281.htm; Glantz SA. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims, November 13, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-8zrx-juh9. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0108; Springer ML, Nabavizadeh P, Mohammadi L. The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes, November 20, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-8zxa-mq9v. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0118; Glantz SA, Lempert LK. Detailed analysis of the Executive Summary (Section 2.7) submitted by Philip Morris International in support of its MRTP application for IQOS, December 9, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-9099-39dy. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0152; Halpern-Felsher B, McKelvey K, Popova L, et al. The evidence cited in PMI's MRTP Application indicates that the proposed labeling and warnings for IQOS will mislead consumers, particularly youth, about the product, December 8, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number:1k1-908n-holz. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0149; Halpern-Felsher B, McKelvey K, Kim M, et al. PMI's MRTP Application for IQOS Does Not Consider IQOS's Appeal to Youth or Adolescents, or the Likelihood that Youth and Adolescents will Initiate Tobacco Use with IQOS or Use IQOS with Other Tobacco Products, December 7, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-9087-458e. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0148; Chun LF, Moazed F, Matthay MA, et al. PMI's MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk, November 30, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number:1k1-9039-d91g. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0133; Chun LF, Moazed F, Matthay MA, et al. IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims, November 30, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number:1k1-903a-mnpl. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0134; St.Helen G, Jacob P, Nardone N, et al. Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application, November 29, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-902j-m8kv. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0129; Max W, Lempert L, Sung H-Y, et al. Philip Morris's Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application, November 22, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-8zy0-6rfg. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0121; Lempert LK, Popova L, Halpern-Felsher B, et al. Because PMI has not demonstrated that IQOS is associated with lower risks, FDA should not permit modified exposure claims, because such claims are likely to be misunderstood as modified risk claims, December 11, 2017. Public Comment, Docket Number: FDA-2017-D-3001, Tracking Number 1k1-90at-5wj2. Available at https://www.regulations.gov/document?D=FDA-2017-D-3001-0154; https://theconversation.com/philip-morris-hides-data-in-plain-sight-on-dangers-of-new-heat-not-burn-product-87636.

of cigarette smoke. Specifically, Garcia-Arcos and colleagues[2] exposed adult mice to the aerosol of saline, nicotine-free, or nicotine-containing e-liquid for 4 months and found that only the nicotine-laden aerosol increased airway and alveolar cell death and airspace enlargement reminiscent of COPD. Similarly, a 2018 study[3] reported that rats exposed to either subcutaneous nicotine or e-cigarette nicotine-containing aerosol for 5 weeks (achieving plasma nicotine concentrations comparable to habitual cigarette smokers) suffered emphysematous airspace enlargement and loss of lung vascular elements. ***Thus, animal studies in two different species are consistent with nicotine having direct pulmonary toxicity.***

Many important questions are raised by these findings, including: (a) To what extent are these findings generalizable to humans? (b) Does inhalational as compared to systemic nicotine have the same spectrum of toxicity? (c) What will be the lung health impact of increased dual use of combustible cigarettes and nicotine-laden aerosols from e-cigarettes (or other inhaled nicotine products such as heated tobacco products)? (d) Are adolescents with still-growing lungs at increased risk for nicotine-mediated pulmonary toxicity given the substantial literature implicating nicotine in disrupting lung development in animal models and humans?[4]

Increasing evidence demonstrates that components of e-cigarette aerosol may have a unique spectrum of toxicity relative to combusted cigarettes secondary to aerosolized propylene glycol,[5]

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[2] Garcia-Arcos, I. et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax 2016; 71: 1119–1129.

[3] Reinikovaite, V. et al. The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke. Eur. Respir. J. 2018;51(4). pii: 1701661. doi: 10.1183/13993003.01661-2017. Print 2018 Apr.

[4] England, L. J. et al. Developmental toxicity of nicotine: A transdisciplinary synthesis and implications for emerging tobacco products. Neurosci. Biobehav. Rev. 2017; 72: 176–189).

[5] Wieslander, G., Norbäck, D. & Lindgren, T. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. Occup. Environ. Med. 2001; 58: 649–655.
Konrádová, V., Vávrová, V. & Janota, J. Effect of the inhalation of a surface tension-reducing substance (propylene glycol) on the ultrastructure of epithelium of the respiratory passages in rabbits. Folia Morphol. 1978; 26, 28–34.
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Werley, M. S. et al. Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. Toxicology 2011; 287: 76–90.
Varughese, S. et al. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. Am. J. Ind. Med. 2005; 47: 411–418.

flavorants including diacetyl,[6] and metals.[7] Studies have also unexpectedly found harmful flame retardant chemicals (used in the production of plastic e-cigarette casings) in the aerosol[8] and the urine of users.[9]

Recent work reveals that e-cigarette users have major changes in the lung proteome,[10] and case reports of unique lung toxicity are accumulating.[11] Remarkably, a recent study showed that

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Farsalinos, K. E., Kistler, K. A., Gillman, G. & Voudris, V. Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins. Nicotine Tob. Res. 2015; 17: 168–174.
Behar, R. Z. et al. Identification of Toxicants in Cinnamon-Flavored Electronic Cigarette Refill Fluids. Toxicol. Vitro Int. J. Publ. Assoc. BIBRA 2013; doi:10.1016/j.tiv.2013.10.006
Behar, R. Z. et al. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. Tob. Control tobaccocontrol-2016-053224. (2016;. doi:10.1136/tobaccocontrol-2016-053224
Romagna, G. et al. Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. Inhal. Toxicol. 2013; 25: 354–361.
Farsalinos, K. E. et al. Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. Int. J. Environ. Res. Public. Health 2013; 10: 5146–5162.
Bahl, V. et al. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod. Toxicol. Elmsford N 2012; 34: 529–537.
Kosmider, L. et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. Thorax 2016;. doi:10.1136/thoraxjnl-2015-207895
[7]Olmedo, P. et al. Metal Concentrations in e-Cigarette Liquid and Aerosol Samples: The Contribution of Metallic Coils. Environ. Health Perspect. 2018; 126, 027010.
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Hess, C. A. et al. E-cigarettes as a source of toxic and potentially carcinogenic metals. Environ. Res. 2017; 152: 221–225.
Lerner, C. A. et al. Electronic cigarette aerosols and copper nanoparticles induce mitochondrial stress and promote DNA fragmentation in lung fibroblasts. Biochem. Biophys. Res. Commun. 2016; 477: 620–625.
[8] Chung, S.-S., Zheng, J.-S., Kwong, A. C. S. & Lai, V. W. Y. Harmful flame retardant found in electronic cigarette aerosol. J. Clean. Prod. 2018; 171, 10–16.
[9] Wei, B., Goniewicz, M. L., O'Connor, R. J., Travers, M. J. & Hyland, A. J. Urinary Metabolite Levels of Flame Retardants in Electronic Cigarette Users: A Study Using the Data from NHANES 2013-2014. Int. J. Environ. Res. Public. Health 2018; 15 <<citation needs completion>>..
[10] Ghosh, A. et al. Chronic E-cigarette Exposure Alters the Human Bronchial Epithelial Proteome. Am. J. Respir. Crit. Care Med. 2018; doi:10.1164/rccm.201710-2033OC
[11] Khan, M. S. et al. Organizing pneumonia related to electronic cigarette use: A case report and review of literature. Clin. Respir. J. 2018; 12: 1295–1299.
McCauley, L., Markin, C. & Hosmer, D. An unexpected consequence of electronic cigarette use. Chest 2012; 141: 1110–1113.
Hureaux, J., Drouet, M. & Urban, T. A case report of subacute bronchial toxicity induced by an electronic cigarette. Thorax 2014; 69: 596–597.
Thota, D. & Latham, E. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor. J. Emerg. Med.2014: 47: 15–17.

chronic exposure to e-cigarette aerosol in mice caused multi-organ fibrosis,[12] demonstrating that whole-body toxicological assessments of these novel devices will be essential going forward.

Consistent with these animal results, a cross-sectional analysis of Wave 1 of the PATH dataset found that current (daily or nondaily) e-cigarette users were nearly twice as likely to have been diagnosed with COPD (including COPD, chronic bronchitis, or emphysema) than people who did not use e-cigarettes (adjusted odds ratio, 1.86; 95% CI, 1.22-2.83).[13] This study controlled for other tobacco product usage and secondhand smoke exposure using propensity score matching.

Given the potential pulmonary toxicity of nicotine alone, and the growing body of literature on the adverse health effects of e-cigarettes, it is essential that the FDA not make policies regarding reduction of nicotine in combustible tobacco products on the assumption that e-cigarettes are substantially safer than conventional cigarettes to avoid the unintended consequence of supplanting one form of nicotine-mediated lung toxicity for another.

Cardiovascular Effects

Both e-cigarettes and conventional cigarettes deliver ultrafine particles that are 1-2 orders of magnitude smaller than a human hair,[14] which in smoke and air pollution increase risk of cardiovascular disease and acute myocardial infarction with a nonlinear dose-response curve.[15] Myocardial infarction risk drops when people stop smoking conventional cigarettes or stop being exposed to secondhand smoke.[16] E-cigarette and traditional cigarette smoking in healthy smokers

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[12] Crotty Alexander, L. E. et al. Chronic Inhalation of E-Cigarette Vapor Containing Nicotine Disrupts Airway Barrier Function and Induces Systemic Inflammation and Multi-Organ Fibrosis in Mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2018; doi:10.1152/ajpregu.00270.2017

[13] Perez MF, Atuegwu N, Mead E, Oncken C, Mortensen EM. E-cigarette use is associated with emphysema, chronic bronchitis and COPD. Presented at: American Thoracic Society 2018 International Conference; May 18-23, 2018; San Diego, CA. Poster 402. https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A6245

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Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. Nicotine Tob Res. 2014; 16(10):1319-1326 doi:10.1093/ntr/ntu078

[15] Pope CA, 3rd, Burnett RT, Krewski D, et al. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. Circulation. 2009; 120(11):941-948 doi:10.1161/CIRCULATIONAHA.109.857888

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[16] Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. Circulation. 1997; 96(4):1089-1096

with no known cardiovascular disease exhibit similar inhibition of endothelial function as measured by flow mediated dilation of arteries, shift in cardiac autonomic balance toward sympathetic predominance, and increased oxidative stress, which are associated with increased cardiac risk.[17] There is also increased oxidative stress in both e-cigarette users and conventional cigarette smokers.[18] Laboratory studies done with e-cigarette extracts found that e-cigarette use increases the release of inflammatory mediators from keratinocyte, alveolar epithelial cell lines and neutrophils.[19] E-cigarette aerosol also induces platelet activation, aggregation, and adhesion.[20] In mice, chronic whole body exposure to e-cigarette aerosol accelerates aortic stiffness, significantly impairs aortic endothelial function, and may lead to impaired cardiac function.[21] These observations lead to concerns that e-cigarette use would be associated with increased risk of acute myocardial infarction.

Alzahrani et al[22] used the National Health Interview Surveys of 2014 (n=36,697) and 2016 (n=33,028) to examine the cross-sectional association between e-cigarette use (never, former, some days, daily) and cigarette smoking (same categories) and myocardial infarction in a single logistic regression model that also included demographics (age, gender, BMI) and health characteristics (hypertension, diabetes, and hypercholesterolemia) using logistic regression. (Because this is a cross-sectional study the timing of e-cigarette use and the myocardial infarction is not known.) Daily e-cigarette use was independently associated with increased odds of having had a myocardial infarction (OR=1.79, 95% CI=1.20, 2.66, p=0.004) as was daily conventional cigarette smoking (OR=2.72, 95% CI=2.29, 3.24, p<0.001). Former and some day e-cigarette use were not significantly associated with having had a myocardial infarction (p=0.608 and p=0.392) whereas former (OR=1.70, p<0.001) and some day cigarette smoking (OR=2.36, p<0.001) were. Odds of a myocardial infarction were also increased with history of hypertension (OR=2.32, p<0.001), high cholesterol (OR=2.36, p<0.001), and diabetes (OR=1.77,

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Tan CE, Glantz SA. Association between smoke-free legislation and hospitalizations for cardiac, cerebrovascular, and respiratory diseases: a meta-analysis. Circulation. 2012; 126(18):2177-2183 doi:10.1161/CIRCULATIONAHA.112.121301

[17] Carnevale R, Sciarretta S, Violi F, et al. Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. Chest. 2016; 150(3):606-612 doi:10.1016/j.chest.2016.04.012

Moheimani RS, Bhetraratana M, Yin F, et al. Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk. JAMA Cardiol. 2017; 2(3):278-284 doi:10.1001/jamacardio.2016.5303

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[18] Carnevale R, Sciarretta S, Violi F, et al. Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. Chest. 2016; 150(3):606-612 doi:10.1016/j.chest.2016.04.012

[19] Higham A, Rattray NJ, Dewhurst JA, et al. Electronic cigarette exposure triggers neutrophil inflammatory responses. Respir Res. 2016; 17(1):56 doi:10.1186/s12931-016-0368-x

[20] Hom S, Chen L, Wang T, Ghebrehiwet B, Yin W, Rubenstein DA. Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. Platelets. 2016; 27(7):694-702 doi:10.3109/09537104.2016.1158403

[21] Olfert IM, DeVallance E, Hoskinson H, et al. Chronic exposure to electronic cigarette (E-cig) results in impaired cardiovascular function in mice. J Appl Physiol (1985). 2017:jap 00713 02017 doi:10.1152/japplphysiol.00713.2017

[22] Alzahrani,T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. Am. J. Prev. Med. (in press)

p<0.001) and age (OR=1.65 per 10 years, p<0.001). Women (OR=0.47, p<0.001) had lower odds of having had a myocardial infarction. Thus, daily e-cigarette use, adjusted for smoking conventional cigarettes as well as other risk factors, is associated with increased risk of myocardial infarction.

The finding that dual use of e-cigarettes and conventional cigarettes is more dangerous than use of either product alone is of particular concern in the context of this ANPRM because a policy that simply reduced cigarette or other tobacco product consumption when users add other inhaled tobacco products could result in net public health harm.

(2) If FDA were to issue a product standard setting a maximum nicotine content for cigarettes, would smokers seek to add liquid nicotine to their VLNC cigarettes? Therefore, should such a regulation include provisions prohibiting the sale or distribution of any tobacco product designed for the purposes of supplementing the nicotine content of a combusted tobacco product (or any product where the reasonably foreseeable use is to supplement this nicotine content)? How could such a provision be structured to efficiently and effectively achieve this purpose? Should FDA consider other means to prevent supplementing the nicotine content of a combusted tobacco product subject to a nicotine tobacco product standard?

Yes. The availability of such products would effectively nullify the intent of the product standard, which is to move people away from regulated combusted products.

(3) Would a nicotine tobacco product standard affect the current illicit trade market, and, if so, to what extent? How would users obtain their sources of tobacco in an illicit market? How would manufacturers distribute their illicit products and develop consumer awareness of such products? How would such sales take place?

As described in detail in our public comment on illicit trade,[23] the major cigarette companies have a long well-documented history of participating in the illicit market to avoid taxation, other tobacco control laws and regulations, and to open markets***. The FDA needs to be cognizant of this history and accompany any new product standard with strong rules and enforcement to prevent the tobacco companies from taking such actions.***

The recent paper by Gilmore et al[24] details extensive efforts by the tobacco companies to use illicit trade to avoid taxes and undermine other tobacco control policies by co-opting and undermining the enforcement process. The abstract of their paper summarizes these issues:

> BACKGROUND: The Illicit Trade Protocol (ITP) requires a global track and trace (T&T) system to reduce tobacco smuggling. Given the tobacco industry's (TI) historical

[23] Crosbie E, Bialous S, Lempert L, Glantz SA. To minimize illicit tobacco trade, FDA should reject any partnership with the tobacco industry, reject industry estimates and exaggeration of illicit trade, and use the FCTC Protocol on Illicit Trade as a model to counter the supply side of illicit trade. Docket No. FDA-2018-N-0529. May 30, 2018. https://www.regulations.gov/searchResults?rpp=25&po=0&s=1k2-93fq-

[24] Gilmore AB, Gallagher AWA, Rowell A. Tobacco industry's elaborate attempts to control a global track and trace system and fundamentally undermine the Illicit Trade Protocol. Tob Control. 2018 Jun 13. pii: tobaccocontrol-2017-054191. doi: 10.1136/tobaccocontrol-2017-054191. [Epub ahead of print]

involvement in tobacco smuggling, it stipulates that T&T 'shall not be performed by or delegated to the tobacco industry'. This paper explores the rationale for & nature of the TI's effors to influence the ITP & its T&T system.
METHODS: Analysis of leaked TI documents and publicly available data, investigation of front groups, trademark and patent ownership.
FINDINGS: Growing & diverse sources of evidence indicate that the TI remains involved in tobacco smuggling and that TI cigarettes account for around two-thirds of the illicit cigarette market. The TI therefore has a vested interest in controlling the global T&T system aimed to curtail this behaviour. To this end, Philip Morris International (PMI) adapted its pack marker system, Codentify, to meet T&T requirements, licensed it for free to its three major competitors who then collectively promoted it to governments using front groups and third parties including companies claiming to be independent despite clear TI links. PMI also sought to suggest Codentify was independent by selling some parts of its intellectual property on Codentify while retaining others, leaving a complex web of shared interests. In Africa, British American Tobacco used payments to obtain data suggesting its smaller competitor companies were evading taxes and secure influence with tax authorities. Regulatory capture has been enhanced by a public relations effort involving TI funding for conferences, training, research, and international police and anti-corruption organisations. Collectively this has created public messaging and a powerful network of organisations supportive of the TI's misleading position on illicit.
CONCLUSIONS: Governments should assume the TI seeks to control T&T systems in order to avoid scrutiny and minimise excise tax payments and that any T&T system based on Codentify, on intellectual property currently or previously owned by the TI, or being promoted or implemented by companies with TI links, is incompatible with the ITP and would not serve to reduce illicit trade.

While this paper was written in terms of international issues, particularly around taxation, precisely the same issues and likely industry behavior can be anticipated if the FDA develops and implements a nicotine product standard.

In particular, the actual risk of increasing demand for non-conforming products in the illicit market following adoption of a product standard will be highly dependent on the final standard adopted and the timeline for implementation. ***As these tobacco product standards are developed and implemented, it will be necessary for the FDA to prepare to respond to tobacco industry claims that the standard will increase demand for illicit products***.[25]

In particular, Family Smoking Prevention and Tobacco Control Act (FSPTCA) section 907(a)(3) gives FDA the authority to establish tobacco product standards that are "appropriate for the protection of the public health." In addition to considering scientific evidence concerning the risks and benefits of the proposed standard to the population as a whole, including users and nonusers of tobacco products, FSPTCA section 907(b)(2) requires FDA to consider the "countervailing effects" of the tobacco product standard on population health, such as "the

[25] Joossens L, Raw M. Turning off the tap: the real solution to cigarette smuggling. Int J Tuberc Lung Dis. 2003 Mar;7(3):214-22.

creation of a significant demand for contraband or other tobacco products" that do not meet FDA's tobacco product requirements and "the significance of such demand."[26]

Since it is required for the FDA to consider the possibilities of illicit trade in its rulemaking, the FDA should use its considerable authority to discourage illicit trade, rather than relying on the regulated tobacco companies to voluntarily reign in illicit trade. The FDA should:

1) Reject any partnership with the tobacco industry
2) Reject industry estimates and exaggeration of illicit trade
3) Use FCTC Protocol on Illicit Trade as model to counter the supply side of illicit trade

(4) FDA hypothesizes that, based on currently available research, nicotine levels like those levels that FDA would consider with a possible nicotine tobacco product standard would be self-limiting (i.e., smokers would be unable to obtain their nicotine dose from cigarettes no matter how they smoke them and eventually would stop trying to do so). Do any peer-reviewed studies demonstrate that lowering the nicotine content of cigarettes to minimally addictive levels might encourage consumers to smoke more VLNC cigarettes to achieve the higher nicotine doses currently delivered by NNC cigarettes?

All studies to date indicate that smokers dislike reduced nicotine content cigarettes. As discussed in Part 1 of this public comment, smokers who are switched to cigarettes containing 0.4 mg nicotine/gram tobacco smoke fewer cigarettes per day compared to those smoking their own brand or high nicotine research cigarettes. However, with gradual reduction there is a small increase in cigarettes per day when nicotine content is moderately reduced (5 mg nicotine/gm tobacco).[27] Some smokers experience nicotine withdrawal symptoms during nicotine reduction. Notably non-compliance with research cigarettes is common, although not many non-study cigarettes are smoked per day. Smokers appear to be smoking their usual cigarettes when they have a desire for nicotine. There is evidence that compliance with reduced nicotine content cigarettes is enhanced when non-combustible nicotine products are readily available.

(5) If a nicotine tobacco product standard were in effect, the following outcomes could occur: (1) Smokers could continue to smoke but use the low nicotine products; (2) smokers could completely switch to, or dual use low nicotine products with, other legal

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[26] U.S. Food and Drug Administration. Family Smoking Prevention and Tobacco Control Act. Washington D.C., United States, 22 June 2009. Available at: https://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm246129.htm. Accessed 25 May 2018.

[27] Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes.Cancer Epidemiol Biomarkers Prev. 2012 May;21(5):761-9. doi: 10.1158/1055-9965.EPI-11-0644. Epub 2012 Feb 21.
Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. Cancer Epidemiol Biomarkers Prev. 2007 Nov;16(11):2479-85.
Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized Trial of Reduced-Nicotine Standards for Cigarettes. N Engl J Med. 2015 Oct;373(14):1340-9. doi: 10.1056/NEJMsa1502403.

tobacco or nicotine products; (3) smokers could quit using any nicotine or tobacco product; or (4) smokers could seek to buy illegal cigarettes in an illicit market. Are there data that would provide information on which of these outcomes is most likely? Is there some other outcome that could occur?

It is plausible that any or all of these outcomes could occur. Which of these outcomes occurs will depend on the details of the product standard and how it is implemented and enforced.

In addition, an implicit assumption that pervades current FDA nicotine policy (and the framing of this question) is that there is a substantial "hard core" of smokers who cannot or will not stop smoking and so there is a substantial irreducible need for a source of chronic self-administration of recreational nicotine.[28] The empirical evidence to date does not support this assumption. Over time, as smoking prevalence has declined, cigarette consumption among the remaining smokers has declined and quit attempts have increased, indicating that the population of smokers is softening not hardening. This pattern exists among the general population[29] and among people with mental illness who smoke at much higher rates than the general population.[30] It is important that FDA not undermine this process.

Equally important, most smokers could quit without the use of alternative sources of nicotine.[31] In fact, quitting "cold turkey" is the most common way that people quit smoking. It is crucial that the FDA recognize this fact and ensure that any nicotine product standard not inadvertently undermine smoking and other tobacco cessation that does not involve the use of nicotine products.

(6) If an illicit market developed, what percentage of current smokers would switch to illicit conventional cigarettes rather than quitting or switching to other legal products? How would this change if illicit conventional cigarettes were more expensive and/or harder to obtain? How would this change with the implementation of improved

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[28] Gottlieb S, Zeller M. A Nicotine-Focused Framework for Public Health. N Engl J Med. 2017 Sep 21;377(12):1111-1114. doi: 10.1056/NEJMp1707409. Epub 2017 Aug 16.

[29] Kulik M, Glantz S. The smoking population in the USA and EU is softening not hardening. Tob Control. 2016 Jul;25(4):470-5. doi: 10.1136/tobaccocontrol-2015-052329. Epub 2015 Jun 24.

[30] Kulik M, Glantz S. Softening Among U.S. Smokers With Psychological Distress: More Quit Attempts and Lower Consumption as Smoking Drops. Am J Prev Med. 2017 Dec;53(6):810-817. doi: 10.1016/j.amepre.2017.08.004. Epub 2017 Oct 10.

[31] Smith AL, Carter SM, Dunlop SM, Freeman B, Chapman S. The views and experiences of smokers who quit smoking unassisted. A systematic review of the qualitative evidence. PLoS One. 2015 May 26;10(5):e0127144. doi: 10.1371/journal.pone.0127144. eCollection 2015.
Smith AL, Carter SM, Chapman S, Dunlop SM, Freeman B. Why do smokers try to quit without medication or counselling? A qualitative study with ex-smokers. BMJ Open. 2015 Apr 30;5(4):e007301. doi: 10.1136/bmjopen-2014-007301.
Smith AL, Chapman S. Quitting smoking unassisted: the 50-year research neglect of a major public health phenomenon. JAMA. 2014 Jan 8;311(2):137-8. doi: 10.1001/jama.2013.282618.
Chapman S, Wakefield MA. Large-scale unassisted smoking cessation over 50 years: lessons from history for endgame planning in tobacco control. Tob Control. 2013 May;22 Suppl 1:i33-5. doi: 10.1136/tobaccocontrol-2012-050767.

monitoring and enhanced enforcement by FDA and its partners?

The response to this question will depend heavily on how effectively FDA uses its authority to prevent the emergence of an illicit market. See response to question 6(3).

(7) If a nicotine tobacco product standard prompted growth of an illicit market, how long would it likely last? Would demand likely decrease over time, stay the same, or increase?

The response to this question will depend heavily on how effectively FDA uses its authority to prevent the emergence of an illicit market. See response to question 6(3).

(8) If a nicotine tobacco product standard prompted growth of an illicit market, what effect, if any, would this have on the market for illegal drugs? Are there data showing a relationship between illicit tobacco use and illegal drug use?

The multinational tobacco companies have a history of working with organized crime, including drug cartels:

> … in some cases, the manufacturers have worked directly with organized crime figures. In Colombia, tobacco companies are alleged to have helped launder drug money and to have worked closely with distributors who are involved in drug trafficking. A Colombian lawsuit against Philip Morris and BAT accuses them of involvement in drug-money laundering through what is known as the "black market peso exchange," a circuitous system by which drug dollars are laundered for clean pesos through the purchase and importation of such goods as cigarettes and alcohol. In a federal civil racketeering lawsuit launched in 2000, Colombia's governors accused tobacco company executives of illegally entering the country to organize smuggling networks and retrieve cash payments, which were then smuggled out for deposit in offshore banks. Company employees are also alleged in the lawsuit to have bribed border guards. And their agents have been implicated in illegal cash campaign contributions to Colombia's former president Ernesto Samper.
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> In Italy, court cases and police and government reports reveal an intricate web of Mafia families that through bribery, intimidation, and murder control the smuggling of billions of Philip Morris and R.J. Reynolds cigarettes into Europe through Cyprus, Albania, and Montenegro. In Spain, at least one major distributor for RJR is allegedly a black market distributor linked to illegal drug trafficking. In Canada, RJR sales executives dealt directly with smugglers linked to the American and Canadian mafia. In some cases, tobacco industry executives actively played various gangs off against each other and solicited and received millions of dollars in kickbacks or bribes in return for selling to preferred criminal syndicates, according to court records and sources.[32]

The FDA needs to be cognizant of this history and develop tight independent monitoring of

[32] International Consortium of Investigative Journalists. Tobacco companies linked to criminal organizations in lucrative cigarette smuggling. May 14, 2014. https://www.icij.org/investigations/big-tobacco-smuggling/tobacco-companies-linked-criminal-organizations-lucrative-cigarette-smuggling/

tobacco product production and distribution to block such collaborations from developing in the future.

(9) What mechanisms may be used to prevent, control, or contain illicit markets in conventional cigarettes that may develop if FDA establishes a product standard? What State and Federal entities may be responsible for these mechanisms, and how much would they cost?

See response to question 6(3).

4. OTHER CONSIDERATIONS

(1) What data may be helpful to assess the universe of tobacco products that are currently available to consumers and their relevant characteristics, such as nicotine levels? How can available sources of information, such as manufacturer registrations and/or product listings with FDA, be used in this assessment?

No comment.

(2) How should potential consumer surplus or utility loss from the removal of nicotine in cigarettes be considered, given the availability of other sources of nicotine such as ENDS and the continued availability of combustible tobacco products?

As noted above, the policy should apply to all combusted tobacco products and perhaps all inhaled nicotine products to minimize the possibility that the new product standard will expand or prolong the tobacco epidemic. The FDA's application of the concept of consumer surplus has overstated the "benefits" of smoking and ignored the empirical evidence that smokers regret smoking, a behavior mostly initiated in youth.[33] To the extent that a new product standard helps people break their nicotine addiction, there will be an increase in consumer welfare.

(3) What sources of information could be used to estimate the change in demand for VLNC cigarettes? What factors should we consider in estimating the changes in demand for other tobacco products?

No comment.

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[33] Song AV, Brown P, Glantz SA. When health policy and empirical evidence collide: the case of cigarette package warning labels and economic consumer surplus. Tob Control. 2015 Mar;24(2):112-9. doi: 10.1136/tobaccocontrol-2014-052022. Epub 2014 Dec 30.
Chaloupka FJ, Warner KE, Acemoğlu D, Gruber J, Laux F, Max W, Newhouse J, Schelling T, Sindelar J. An evaluation of the FDA's analysis of the costs and benefits of the graphic warning label regulation. Am J Public Health. 2014 Feb;104(2):e42-51. doi: 10.2105/AJPH.2013.301737. Epub 2013 Dec 12.
Song A, Glantz S. Assessing tobacco regulation: moving beyond economists. Tob Control. 2015 Mar;24(2):123-4. doi: 10.1136/tobaccocontrol-2014-052095. Epub 2015 Jan 6.
Pechacek TF, Nayak P, Slovic P, Weaver SR, Huang J, Eriksen MP. Reassessing the importance of 'lost pleasure' associated with smoking cessation: implications for social welfare and policy. Tob Control. 2017 Nov 28. pii: tobaccocontrol-2017-053734. doi: 10.1136/tobaccocontrol-2017-053734. [Epub ahead of print]

(4) What factors should be considered in estimating changes in experimentation and initiation that may occur as a result of a potential nicotine tobacco product standard?

There should be detailed surveillance of tobacco-related perceptions and behaviors before, during, and after the implementation VLNC products, particularly among youth and other vulnerable populations. This includes assessment of perceived harm, youth susceptibility (willingness to try; curiosity; use expectation), attitudes, and beliefs.

Existing surveillance systems, such as the National Youth Tobacco Survey and Population Assessment of Tobacco and Health, should be fully supported by the FDA to expand measurement of perceptions and behaviors related to VLNC products as they come to market. Because these national surveys are large, complex undertakings, there is also need to conduct more nimble and targeted studies, such as focus groups and Internet or telephone panel surveys to identify potential unexpected or unintended or effects of VLNC products on the likelihood that youth or other vulnerable populations will initiate tobacco product use. Timely identification of how these new products might be perceived will inform appropriate public communication from the FDA to limit misunderstanding or unintended consequences.

Possible misperceptions that could undermine the effectiveness of the VLNC strategy include:

- belief that VLNC cigarettes are safe
- belief that VLNC cigarettes are as effective or more effective for quitting smoking than FDA-approved cessation aids
- perception that VLNC cigarettes are technologically advanced, modern, or exciting
- belief that smoke from VLNC cigarettes is not harmful to others nearby
- belief that clean indoor air laws or other tobacco control policies do not apply to VLNC cigarettes

The FDA must monitor for these or other potential misperceptions so that the public at large has accurate information about VLNC products that does not encourage experimentation or initiation among individuals who otherwise would not have used tobacco or nicotine products. ***The rule should be written in a way that will permit FDA to make adjustments to the standard in response to the surveillance information without going through additional years of rulemaking.***

(5) In what ways might a change in nicotine levels in cigarettes spur innovation in the market for both combusted and noncombusted tobacco products?

The tobacco companies view smoking cessation as a competing brand [34] . Based on past behavior, the tobacco companies can be expected to develop and market new products that will maintain nicotine addiction to prevent smokers from quitting in order to keep their customers.

[34] 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.

The FDA should also consider the advent of new players, exemplified by JUUL, which have led to an explosion of youth use[35] of a product that is nominally sold as an alternative to conventional cigarettes for adult established smokers.

To the extent that the FDA policy facilitates this process, the FDA will contribute to the tobacco epidemic.

(6) What factors should be considered in estimating the impacts of externalities that might exist for VLNC cigarettes, such as secondhand smoke, litter, and pollution? How could the impact of externalities for VLNC cigarettes be compared to the impacts from NNC cigarettes?

Alternative inhaled nicotine products such as e-cigarettes and heated tobacco products involve substantial electronics, plastic and metal cases, and batteries, all of which generate substantial amounts of toxic e-waste.[36] To the extent that consumers are driven to these products, there could be substantial negative environmental consequences. These effects would, to some extent, be offset by fewer cigarette butts. The net effect could be substantial and should be estimated in the regulatory impact analysis and not dismissed as "minor" without a quantitative analysis.

(7) What factors should we consider in estimating the impact of changes in demand for other tobacco products?

See responses to questions 1B(4) and 7(4).

(8) If FDA were to finalize a nicotine tobacco product standard, what might be the costs to current smokers?

See response to question 7(2).

(9) Are there any other relevant comments or information that would be helpful for FDA to consider in analyzing the economic impacts of a proposed nicotine tobacco product standard?

No additional comments.

5. POTENTIAL PUBLIC HEALTH BENEFITS OF PREVENTING INITIATION TO REGULAR USE AND INCREASING CESSATION

Apollonio D, Glantz SA. Tobacco Industry Research on Nicotine Replacement Therapy: "If Anyone Is Going to Take Away Our Business It Should Be Us". Am J Public Health. 2017 Oct;107(10):1636-1642. doi: 10.2105/AJPH.2017.303935. Epub 2017 Aug 17.

[35] Huang J, Duan Z, Kwok J, Binns S, Vera LE, Kim Y, Szczypka G, Emery SL. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. Tob Control. 2018 May 31. pii: tobaccocontrol-2018-054382. doi: 10.1136/tobaccocontrol-2018-054382. [Epub ahead of print]

[36] World Health Organization, Tobacco and its environmental impact: an overview (May 2017). Available at: http://www.who.int/tobacco/publications/environmental-impact-overview/en/

FDA issued an accompanying preliminary impact analysis (http://www.nejm.org/doi/pdf/10.1056/NEJMsr1714617) recognizing potential costs and benefits from a possible nicotine tobacco product standard, including the potential impacts on growers of tobacco and current users of potentially regulated products. FDA's population-based simulation model projects the potential public health impact of enacting a regulation lowering nicotine levels in cigarettes and certain other combusted tobacco products to minimally addictive levels. Based on experts' determinations that the reduction in nicotine levels in combusted tobacco products would create substantial reductions in smoking prevalence due to increased cessation and reduced initiation, the model calculates that by 2100, more than 33 million youth and young adults who would have otherwise initiated regular smoking would not start as a result of the nicotine standard, and 5 million additional smokers would quit smoking one year after implementation of the standard, compared to the baseline scenario, which would increase to approximately 13 million additional former smokers within five years after policy implementation.

This analysis does a good job as far as it goes. However, it considers only tobacco use prevalence and mortality as outcomes. It does not include any measure of impact on health care utilization or costs. The assumptions about transitions between different tobacco use categories include only combusted products, notably excluding electronic cigarettes which are commonly used by cigarette smokers and an important pathway into nicotine addiction for youth, an effect that could be aggravated by a nicotine product standard that does not consider the whole market. The transition rates are derived from the opinions of 8 experts, a reasonable approach given the lack of experience with a low nicotine product. However, the expert opinions vary considerably and do not approach consensus, suggesting great levels of uncertainty in the estimates.

FDA notes that the analysis does not address certain potential added benefits, including: (1) increased quality of life from decreased tobacco-related morbidity and costs savings from medical care averted; (2) impacts of secondhand smoke exposure on public health; (3) reductions in harms caused by smoking-related fires; (4) potential impact on population health from use of other combusted products (e.g., cigars, pipes) if the assumed rule were to cover such products; and (5) potential health benefits associated with smokers cutting down on the number of cigarettes smoked as a result of the standard. These are all important issues that need to be in the final analysis. In addition, the effects of shifting to noncombusted tobacco products (such as e-cigarettes), including their effects on initiation and cessation and their direct health effects needs to be modeled.

All of these questions presume only positive effects of the policy and do not allow for consideration of adverse unintended consequences, such as increases in youth initiation, or shifting current tobacco users to other nicotine products with the net result that overall cessation would be reduced, which is the tobacco companies' goal in the development of new products.

CONCLUSION

A product standard to reduce nicotine delivery in all combustible recreational tobacco products could have unintended negative consequences, such as increasing the demand for and innovation

of other inhaled nicotine products, such as e-cigarettes. The likelihood of increased youth and young adult initiation is of particular concern. ***A reduced nicotine product standard could bring substantial public health benefits if it is done in a way that does not open the door to the tobacco companies to deter cessation and expand their customer base***