Premarket Tobacco Product Applications and Recordkeeping Requirements – Proposed Rule

Docket No: FDA-2019-N-2854

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Introduction

The draft regulation describing information that the FDA requires for successful submission of a PMTA application is thoughtful and covers the full range of issues that the FDA should consider when making a decision as to whether or not allowing the marketing of the new tobacco product would be "appropriate for the protection of public health" (APPH), which is the legal standard for FDA approving a new tobacco product. This public comment provides additional evidence in support of many of the specific aspects of the proposed regulation, as well as suggested changes to make the request for information more precise in a way that would improve the quality of FDA's analyses and decisions.

The rule should require PMTAs to compare new products to *all* products on the market, not just combustible cigarettes

The FDA appropriately describes the purpose of the proposed regulation as requiring an applicant to submit "full reports of information regarding investigations that may show the health risks of the new tobacco product and whether it represents the same or different risks compared to other tobacco products. FDA is proposing to require the submission of these health risk investigations to ensure it understands the full scope of what is known about the potential health risks of the new tobacco product."[1]

This is an appropriate requirement to ensure that any new products granted premarket authorization are appropriate for the protection of the public health (APPH). It is important, however, that any proposed new products be compared to *all* tobacco products on the market at the time the application is submitted. For example, in reaching its decision to grant a PMTA for Philip Morris' IQOS heated tobacco product, the FDA allowed Philip Morris to only compare IQOS to combusted cigarettes, rather than to the full range of tobacco products on the market including e-cigarettes. In the PMTA order, FDA rejected Philip Morris's claim that IQOS produced lower health risks than a conventional cigarette but, nevertheless, issued a market authorization order on the grounds that IQOS produced lower levels of some toxic chemicals than a conventional cigarette. While this is true, FDA discounted the fact that IQOS produces higher levels of other toxic chemicals than in cigarettes. More important, FDA did not consider the fact that IQOS produces higher levels of some toxins than some e-cigarettes currently on the market. ***To avoid similar errors in the future FDA should require applicants to compare their products to* all *other tobacco products on the market***

To implement this change, FDA should amend the proposed rule sections 1114.7(h)(3)(i) and 1114.7(k)(1)(i) by inserting the word "all" before the phrase "other tobacco products."[2] This change would also broaden the categories of products for pharmacological comparisons to include ***all*** products on the market, not simply narrow comparator products similar to the proposed new product. In addition, applicants

[1] FDA, Premarket Tobacco Product Applications and Recordkeeping Requirements, Proposed rule. September 25, 2019. 84 FR 50566 at p. 50567.

[2] For all suggested amendments, see specific section of the proposed rule in the Appendix starting at page 27.

should present evidence on interactions between constituents of the new product and other compounds or drugs to which users may be reasonably exposed. Proposed rule sections 1114.7(k)(ii)(C) should also be amended to reflect that when considering dual use, applicants must analyze whether the new tobacco product will be used in conjunction with one or more of all other products on the market.[3]

In addition, the FDA should change the wording of proposed rule section 1114.27(b)(1)(ii)(B) to indicate that toxicity comparisons need to be made broadly to the universe of all available tobacco products. The new wording should read, "The health risks of the new tobacco product compared to the health risks generally presented by all other products currently on the market."[4] ***This revision will make it clear that this comparison should specifically include other products that have or may have lower risk than the new product to prevent applicants from selecting products known or thought to have higher risks as the comparator products.***

As we have seen with menthol,[5] it is likely that other flavor or vehicle compounds within the new product may interact with each other to cause adverse events and/or increase the likelihood of nicotine addiction. In addition to compounds contained within the product, new products should be required to present evidence that these products do not interfere with pharmaceutical drugs target users may be on. This is especially important in light of publications that indicate interactions between nicotine and chemotherapeutic pharmaceuticals such as: cisplatin,[6] doxorubicine,[7] gemcitabine,[8] camptothecin,[9] 5-

[3] See Appendix, sections 1114.7(h)(3)(i), 1114.7(k)(1)(i), and 1114.7(k)(ii)(C).

[4] See Appendix, section 1114.27(b)(1)(ii)(B).

[5] Benowitz NL, Dains KM, Dempsey D, Havel C, Wilson M, Jacob P 3rd Urine menthol as a biomarker of mentholated cigarette smoking. Cancer Epidemiol Biomarkers Prev. 2010 Dec;19(12):3013-9. doi: 10.1158/1055-9965.EPI-10-0706. Epub 2010 Oct 20.
Hsu PC, Lan RS, Brasky TM, Marian C, Cheema AK, Ressom HW, Loffredo CA, Pickworth WB, Shields PG. Menthol Smokers: Metabolomic Profiling and Smoking Behavior. Cancer Epidemiol Biomarkers Prev. 2017 Jan;26(1):51-60. doi: 10.1158/1055-9965.EPI-16-0124. Epub 2016 Sep 14.
Kramlinger VM, von Weymarn LB, Murphy SE. Inhibition and inactivation of cytochrome P450 2A6 and cytochrome P450 2A13 by menthofuran, β-nicotyrine and menthol. Chem Biol Interact. 2012 May 30;197(2-3):87-92. doi: 10.1016/j.cbi.2012.03.009. Epub 2012 Apr 1..

[6] Do, Nam-Young; Lim, Sung-Chul; A low level of nicotine-induced chemoresistance in a KB cell line. *Molecular medicine Reports*. 1:55-60, 2008
Dasgupta, P.; Kinkade, R.; Joshi, B.; DeCook, C.; Haura, E.; Chellappan, S. Nicotine inhibits apoptosis induced by chemotherapeutic drugs by up-regulating XIAP and surviving. *PNAS*. 103(16):6332-6337. 2006
Arias, LR.; Perry, C.; Yang, L. Real-time electrical impedance detection of cellular activities of oral cancer cells. *Biosensors and Bioelectronics*. 25:2225-2231. 2010

[7] An, Y.; *et al*. Cigarette smoke promotes drug resistance and expansion of cancer stem cell-like side population. *PLOS one*. 7(11). 2011

[8] Banerjee, J.; Al-Wadei, H.; Schuller, H. Chronic nicotine inhibits the therapeutic effects of gemcitabine on pancreatic cancer in vitro and in mouse xenografts. *Eur J Cancer*. 49(5):1152-1158
Banerjee, J.; Al-Wadei, H.; aAl-Wadei, M.; Dagnon, K.; Schuller, H. Differential modulation of nicotine-induced gemcitabine resistance by GABA receptor agonists in pancreatic cancer cell xenografts and in vitro. *BMC Cancer*. 14:725. 2014

[9] Dinicola, S.; *et at*. Nicotine increases survival in human colon cancer cells treated with chemotherapeutic drugs. *Toxocology in Vitro.* 27:2256-2263. 2013

fluorouracil,[10] and etoposide.[11] These interactions range from interfering with the drugs mode of action, creating an environment where these products could reduce the ability of these drugs to fight cancer, to promoting pathways that increase drug resistance mechanisms that may make the drugs effective for a shorter amount of time. These known interactions speak to a need to examine the combined effect of the new product compounds on a wide range of commonly used pharmaceuticals including NSAIDS and anti-depressants in addition to chemotherapeutic and chemo-preventative medications likely to be used by populations switching from a current tobacco product to the new products.

This also a sensitive subpopulations issue discussed elsewhere in this public comment.

Because applicants should be required to compare their new tobacco products to all products currently on the market, and not only to certain products, there is no reason for FDA to require in section 1114.7(c)(3)(iii) and accompanying chart[12] that PMTA applicants provide the product "subcategory." FDA states that this information "is required under sections 910(b)(1)(B) and (G) of the FD&C Act and the proposed rule would require its inclusion in the general information section to help FDA quickly check whether the product is within CTP's purview and identify the specific product that is the subject of the submission."[13] However***, there is no language in section 910(b) of the Family Smoking Prevention and Tobacco Control Act (which lays out the necessary contents of PMTA applications) that requires or even mentions "categories" or "subcategories."***

FDA's June 2019 Guidance on PMTAs similarly states, "Information about tobacco products in the same category or subcategory is important to FDA's evaluation of a tobacco product's potential effect on public health because current users may switch to other products within the same category."[14] However, FDA provides no justification for this observation, and experience in the real world shows that current users may switch to products from different "categories." For example, current cigarette smokers may switch to e-cigarettes, and current e-cigarette users may switch to IQOS or other new products such as nicotine pouches. Therefore, ***FDA should delete the requirement to list product categories and subcategories from proposed rule section 1114.7(c)(3)(iii).***[15]

The rule appropriately requires PMTAs to provide a comprehensive assessment of the available literature related to a new product

Proposed rule section 1114.7(k)[16] appropriately implements the dictates of Tobacco Control Act section 910(b)(1)(A) and requires PMTAs to contain full reports of all information, "both favorable and unfavorable, published or known to, or which should be reasonably known to, the applicant concerning investigations, including nonclinical and human subject studies" which have been made to show the health risks of the product and whether the tobacco products present less risk than other tobacco products. The FDA is acting appropriately when it requires applicants to submit full reports of these investigations,

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[10] Dinicola, S.; *et at*. Nicotine increases survival in human colon cancer cells treated with chemotherapeutic drugs. *Toxocology in Vitro.* 27:2256-2263. 2013

[11] Do, Nam-Young; Lim, Sung-Chul; A low level of nicotine-induced chemoresistance in a KB cell line. *Molecular medicine Reports*. 1:55-60, 2008

[12] See Appendix, section 1114.7(c)(3)(iii) and accompanying chart.

[13] Proposed rule, 84 FR at p. 50579.

[14] FDA, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, Guidance for Industry, June 2019, p. 13.

[15] See Appendix, section 1114.7(c)(3)(iii).

[16] Proposed rule, 84 FR at p. 50650.

regardless of whether they support or are averse to the application, or conducted within or outside the United States.

The FDA appropriately requires applicants to submit information that will allow the FDA to "understand the *full scope* of what is known about the potential health risks of the new tobacco product."[17] This general principle is implemented at several places in the proposed regulation by requiring applicants not only to submit their own studies, but also comprehensive literature reviews of the available literature relevant to the application. ***This is a very important requirement in the proposed regulation because the tobacco industry has a long, well-documented history[18] of conducting biased research or selectively citing studies that serve its interests while ignoring other work that does not serve its interests.***

The final rule should make it explicit that this includes a full literature review of relevant literature. FDA should also amend section 1114.7(k)(2) to require applicants to provide the sources of support (i.e., industry or independent funding) of all studies supporting the industry's application.[19] ***In its assessments of these comparisons the FDA should be cognizant of tobacco companies' long history of manipulating and distorting science and include a specific assessment of why any industry results should be accepted preferentially over independent research which is inconsistently with those industry results in any marketing order granting a PMTA.***

Proposed rule section 1114.7(k)(3)(ii)[20] further strengthens this requirement by requiring not only comprehensive literature reviews, but also "documentation of all actions taken to ensure the reliability of the study," so applicants must demonstrate how the studies provided by industry to support the PMTA compare with the larger scientific literature.

To emphasize the importance of providing FDA with a comprehensive review of the available evidence regarding the proposed new product, FDA should make it clear that FDA *will* consider outside

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[17] Proposed rule, 84 FR at p. 50567.

[18] Velicer C, St. Helen G, Glantz SA. Tobacco papers and tobacco industry ties in *Regulatory Toxicology and Pharmacology,* J Public Health Policy. 2018 February ; 39(1): 34–48. doi:10.1057/s41271-017-0096-6;
Schick SF, Glantz SA. Old ways, new means: tobacco industry funding of academic and private sector scientists since the Master Settlement Agreement. Tob Control. 2007;16(3):157–64;
Garne D, Watson M, Chapman S, Byrne F. Environmental tobacco smoke research published in the journal Indoor and Built Environment and associations with the tobacco industry. Lancet. 2005;365(9461):804–9;
Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA. 1998;279(19):1566–70.
Wertz MS, Kyriss T, Paranjape S, Glantz SA. The toxic effects of cigarette additives. Philip Morris' project mix reconsidered: an analysis of documents released through litigation. PLoS Med. 2011 Dec;8(12):e1001145. doi: 10.1371/journal.pmed.1001145. Epub 2011 Dec 20.
Barnes RL, Hammond SK, Glantz SA. The tobacco industry's role in the 16 Cities Study of secondhand tobacco smoke: do the data support the stated conclusions? Environ Health Perspect. 2006 Dec;114(12):1890-7;
Tong EK, England L, Glantz SA. Changing Conclusions on Secondhand Smoke in a Sudden Infant Death Syndrome Review Funded by the Tobacco Industry. Pediatrics Mar 2005, 115 (3) e356-e366; DOI: 10.1542/peds.2004-1922;
Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. J Alzheimers Dis. 2010;19(2):465-80. doi: 10.3233/JAD-2010-1240.

[19] See Appendix, section 1114.7(k)(2).

[20] Proposed rule, 84 FR at p. 50651.

sources of information during PMTA review, so it is the responsibility of the applicant to provide the FDA with a comprehensive listing of available outside sources of information as well as a specific assessment of how these outside sources and compare with the information included in the application, with particular emphasis on the sources of funding for any studies that are at variance with the applicant's data. ***FDA should therefore amend section 1114.33(a) to add subsection (3) that would provide that FDA will issue a no marketing order if, after considering outside sources of information during PMTA review, FDA finds that the new tobacco product is not appropriate for the protection of the public health.***[21]

Explicit consideration of bias in industry studies

As noted above, the tobacco companies have a long history of funding, either directly or indirectly, research conducted or reported in ways that support industry positions. For example, industry funding is strongly associated with finding no harm of e-cigarettes, compared with studies without a potential conflict of interest (odds ratio 67, 95% confidence interval 8 to 553).[22] In their review of the respiratory effects of e-cigarettes, Gotts et al often found that industry-funded studies produced results more favorable to the industry than independent studies.[23]

A systematic review by Hendlin et al[24] evaluated if industry supported studies (disclosed in the conflict of interest) were more likely to be in favor of tobacco harm reduction (switching to non-cigarette tobacco products) compared to studies that did not receive industry funding. They found that financing from the e-cigarette industry (odds ratio [OR] =20.9; 95% confidence interval [CI]=5.3, 180.7), tobacco industry (OR=59.4; 95% CI=10.1, +infinity), or pharmaceutical industry (OR=2.18; 95% CI=1.3, 3.7) was significantly associated with support for product switching. While 61% of the tobacco harm reduction debate was being carried out over letters and comments, industry funded studies were more likely to be empirical compared to non-industry funded studies. Given that empirical data is more frequently used to inform public health policies, the fact that most empirical data on tobacco harm reduction is industry funded and potentially biased is alarming.

FDA recognizes this problem when it states, "financial conflicts [of] information is important for FDA to consider because it addresses a potential source of bias in investigations. Applicants would be able to use these disclosures as well as appropriate procedures in the design and conduct of the study to demonstrate that a potential bias that may affect the results of the investigation has been minimized. FDA would use the information contained in these disclosures, in conjunction with information about the design and purpose of the study, as well as on-site inspections (if necessary) in its assessment of the reliability of the data."[25] ***This is an important policy, which the FDA should rigorously enforce and address explicitly in any PMTA marketing orders that are issued on the basis of industry research which is in any way incompatible with the larger peer-reviewed literature conducted by independent authorities.***

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[21] See Appendix, section 1114.33(a).

[22] Pisinger C, Godtfredsen N, Bender AM. A conflict of interest is strongly associated with tobacco industry-favourable results, indicating no harm of e-cigarettes. Prev Med2019;119:124-31. doi:10.1016/j.ypmed.2018.12.011 pmid:30576685

[23] Gotts JE, Jordt S-E, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? BMJ 2019; 366 :l5275. https://www.bmj.com/content/366/bmj.l5275.long

[24] Hendlin, Y. H., Vora, M., Elias, J., & Ling, P. M. (2019). Financial Conflicts of Interest and Stance on Tobacco Harm Reduction: A Systematic Review. *Am J Public Health*, e1-e8. doi:10.2105/ajph.2019.305106

[25] Proposed rule, 84 FR at pp. 50608-50609.

Health endpoints

In almost all of the discussions of health endpoints, the FDA begins discussions with cancer and often treats cancer in more detail than other health effects. While cancer is a very important endpoint associated with tobacco use, the fact is that heart and lung disease accounts for more tobacco induced deaths than cancer.[26] The heart and lung disease affects also accrue (and sometimes resolve) more quickly than cancer effects. This means that heart and lung disease effects are more easily directly assessed in the short run than are cancer effects, which take many years to be manifest. Thus, when assessing cancer risks associated with the new product, it may be necessary to rely more heavily on biomarkers of exposure. However, for heart and lung disease, it is entirely feasible to rely on direct measures of biological and clinical effects. For these reasons, while not minimizing the importance of cancer, ***FDA should revise the entire application requirements to give more prominence to heart and lung disease effects.***

Proposed rule section 1114.7(k)(1)(i)(B) requires applicants to provide full reports of all information regarding the toxicological profile of the new tobacco product, including the "genotoxicity, carcinogenicity, reproductive toxicity, immunotoxicity, acute toxicity, and repeat dose (chronic) toxicity of the new tobacco product…" ***The rule should be amended[27] to require applicants to prioritize submission of information regarding the cardiovascular and respiratory effects of the new tobacco product. In addition, effects on blood should be included in the cardiovascular section. Intergenerational health effects caused by epigenetic changes should also be included in the list.***

FDA should not assume that the health effects of any proposed new product will be reductions in serious medical conditions and premature mortality

When discussing the proposed rule section 1114.7(l) requirements for presenting evidence of the effect of the new product on the population as a whole, FDA states, "relevant outcomes measures could include reductions in serious medical conditions and premature mortality and gains in life-years lived in the population."[28] While this would ideally be the case for any new product that warranted being granted a PMTA marketing order, it is by no means certain. In addition, it is possible that a new product might reduce one kind of adverse health effects while increasing another. (For example, the animal toxicology studies that Philip Morris submitted as part of the IQOS MRTP application indicated liver toxicity associated with IQOS that was not observed with a cigarette.[29]) Proposed rule section 1114.7(l) appropriately requires the application to "provide an overall assessment of the likely effect that the marketing of the tobacco product may have on overall tobacco-related *morbidity and mortality*. [emphasis added]" Indeed, when considering population health effects, the impact of the new product on morbidity as well as mortality is essential.[30]

FDA should thoroughly review the entire draft regulation to ensure that there are no assumptions about the effects of new products embodied in the wording of the regulation.

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[26] Roversi S, Fabbri LM, Sin DD, Hawkins NM, Agusti A. Chronic obstructive pulmonary disease and cardiac diseases: an urgent need for integrated care. Am J Respir Crit Care Med 2016;194:1319–1336.
[27] See Appendix, section 1114.7(k)(1)(i)(B).
[28] Proposed rule, 84 FR at p. 50610.
[29] Chun L, Moazed F, Matthay M, Calfee C, Gotts J. Possible hepatotoxicity of IQOS. Tob Control. 2018 Nov;27(Suppl 1):s39-s40. doi: 10.1136/tobaccocontrol-2018-054320. Epub 2018 Aug 21. No
[30] Max W, Sung HY, Lightwood J, Wang Y, Yao T. Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. Tobacco Control 2018;27 (suppl 1): S82-S86. PMCID: PMC6240026.

Health effects studies should consider sensitive subpopulations

It is common in tobacco health effects research to assess the effects of tobacco use on healthy individuals. While this is an important issue that needs to be addressed in any PMTA application, it is equally important to assess the effects of using any new tobacco product on people who are already compromised, such as people with pre-existing cardiovascular or pulmonary disease or cancer, as well as less serious existing conditions such as being exposed to the flu. For example, levels of exposure to cigarette smoke and e-cigarette aerosol that have limited effects in healthy individuals have much more serious pulmonary impact on people exposed to other forms of lung inflammation, including bacterial and viral pneumonia.[31]

FDA should also require that impacts on susceptible subpopulations be explicitly considered in any mathematical models or simulations used to argue that the net effect of issuing a PMTA marketing order will be positive.

The FDA is correct to require applicants to present evidence on whether the new tobacco product would deter people who would otherwise have quit all tobacco use from doing so

Proposed rule section 1114.7(k)(1)(ii)(F) appropriately requires applicants to submit full reports on how the product and its labeling and advertising will affect "the likelihood that current tobacco users who may have otherwise quit using tobacco products will instead start or continue to use the product."[32]

This requirement is especially important because, in contrast to public rhetoric from the tobacco industry focusing on the development of new products for "harm reduction," internal industry marketing research and planning documents for the development of e-cigarettes,[33] heated tobacco products,[34] and industry promoted forms of nicotine replacement therapy[35] all frame the development of these products as an alternative to quitting tobacco entirely. The tobacco companies view quitting as a competing product to their products and develop these new products to compete with quitting. The development of new products is part of tobacco companies' plans to reframe themselves as nicotine pharmaceutical companies, and to reframe nicotine products as benign and socially acceptable.[36]

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[31] Moazed F, Burnham EL, Vandivier RW, et al. Cigarette smokers have exaggerated alveolar barrier disruption in response to lipopolysaccharide inhalation. Thorax 2016;71:1130-1136;
Calfee, C. S. et al. Active and passive cigarette smoking and acute lung injury after severe blunt trauma. Am. J. Respir. Crit. Care Med.2011; 183, 1660–1665.

[32] Proposed rule, 84 FR at p. 50651.

[33] 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.

[34] Elias J, Dutra LM, St Helen G, Ling PM. Revolution or redux? Assessing IQOS through a precursor product. Tob Control. 2018 Nov;27(Suppl 1):s102-s110. doi: 10.1136/tobaccocontrol-2018-054327. Epub 2018 Oct 10.

[35] 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.

[36] Hendlin YH, Elias J, Ling PM. The Pharmaceuticalization of the Tobacco Industry. Ann Intern Med. 2017 Aug 15;167(4):278-280. doi: 10.7326/M17-0759. PMCID: PMC5568794;
Ling PM, Glantz SA. Tobacco company strategies to identify and promote the benefits of nicotine. Tob Control. 2019 May;28(3):289-296. PMCID: PMC6368903.

FDA should specifically require copies of all marketing research related to the development of any proposed new product, as well as the predicate products that industry may have developed in earlier years and not taken to market, to specifically deal with the positioning of these products as a competitor to quitting.

Dual and poly use should be given more emphasis

While the FDA appropriately discusses the importance of dual and poly tobacco product use throughout the proposed regulation, this language needs to be strengthened and made more explicit to ensure that applicants adequately address this common behavior. For example, in the IQOS PMTA materials, FDA allowed Philip Morris to consider 70% use of IQOS to be "complete switching" from conventional cigarettes.[37] And given the nonlinear dose-response for cardiovascular and other health effects, 30% of tobacco consumption being from conventional cigarettes would be enough to confer essentially the same health risks of being a heavy smoker. FDA should require that any assessment or assumption of "switching" should require that all nicotine consumption was coming from the new product.

Proposed rule section 1114.7(k)(1)(i)(D) should be strengthened[38] to require submission of meaningful estimates of true levels of dual and poly use based on research for the proposed product or comparable products in an assessment of the health impacts of dual use. This is particularly important because several studies of cardiovascular and pulmonary effects of e-cigarettes have shown that dual use is more dangerous than smoking alone.[39]

Likewise, FDA should require biological and exposure information about the most common forms of actual or anticipated dual use. For example, proposed rule section 1114.7(k)(1)(i)(B) requires applicants to submit a toxicological profile that "includes information on the toxicity of the ingredients, additives, and HPHCs, relative to the route of administration and the range of potential levels of exposure resulting from the use of, or exposure to, the new tobacco product…" Because dual use is highly likely, it is important that the applicant also provide comparable information for dual users, because the net effect could be to increase the amount or number of toxicants to which the user is exposed. The rule should be amended to require this information.[40] In addition, the biological and clinical effects of dual exposure could be higher or different than exposure to the new product alone.

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[37] FDA, PMTA Coversheet: Technical Project Lead Review (TPL), p. 72. April 29, 2019. Available at: https://www.fda.gov/media/124247/download.

[38] See Appendix, section 1114.7(k)(1)(i)(D).

[39] Alzahrani T, Pena I, Temesgen N, Glantz SA. Association Between Electronic Cigarette Use and Myocardial Infarction. Am J Prev Med. 2018 Oct;55(4):455-461. doi: 10.1016/j.amepre.2018.05.004. Epub 2018 Aug 22. Erratum in: Am J Prev Med. 2019 Oct;57(4):579-584.
Bhatta DN, Glantz SA. Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health. J Am Heart Assoc. 2019 Jun 18;8(12):e012317. doi: 10.1161/JAHA.119.012317. Epub 2019 Jun 5. Erratum in: J Am Heart Assoc. 2019 Nov 5;8(21):e002313.
Wills TA, Pagano I, Williams RJ, Tam EK. E-cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. 2019 Jan 1;194:363-370. doi: 10.1016/j.drugalcdep.2018.10.004. Epub 2018 Nov 7.
Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, Nasir K, Blaha MJ. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. Am J Med. 2019 Aug;132(8):949-954.e2. doi: 10.1016/j.amjmed.2019.02.016. Epub 2019 Mar 8.

[40] See Appendix, section 1114.7(k)(1)(i)(B).

The requirements for the issuance of a no marketing order (proposed rule section 1114.33) should be revised[41] to explicitly include dual use and deterrence of complete quitting of all tobacco products as factors that FDA explicitly must consider when deciding if there is a lack of a showing that permitting the product to be marketed would be APPH.

FDA should require applicants to report information about use of newly deemed products that have been on the market prior to the deadline for submitting a PMTA

The regulation is written assuming that a new product has not yet been on the market. While this is a reasonable assumption going forward, the reality is that newly deemed products under the 2016 "deeming rule" have been on the market for several years, resulting in substantial evidence about actual use patterns and health effects. The FDA should explicitly require that this information be included in any PMTA application for a product that was already on the market prior to submitting the application, even if the product that is the subject of the PMTA application is different from products that were on the market prior to submitting the PMTA application. Proposed rule section 1114.7(k)(1) should be amended[42] to require this information.

Proposed rule section 1114.7(d)(4)[43] requires applications to include a description of problems that were previously identified, including: "if there are previous or similar versions [of the proposed new product] that are the subject of studies in the application or were marketed, the application must contain a bibliography of all reports regarding the previous or similar version of the product, whether adverse or supportive." This is an important requirement that should be maintained.

FDA should require that all studies submitted in support of a PMTA be adequately powered

There are several places in the proposed regulation where FDA requires applicants to submit studies related to product testing, exposure, or biological and clinical effects. In many places the applicants will have a strong incentive to report null findings, i.e., that there is no significant elevation in some adverse exposure. Interpreting such null findings requires knowing the power of the study in question to detect a meaningful effect. It is well-established in statistics that having a sample size which is too small will lead to nonsignificant results.

Proposed rule section 1114.7(i)(4)[44] recognizes this fact implicitly and requires that each product testing and analysis "must be conducted using a sufficient sample size and number of replicates to substantiate the results of the type of testing conducted" and requires the applicant to provide information on the number of samples, the method procedure, method validation information and rationale for selecting each test method, test protocols, quantitative acceptance criteria, and other information. While this is a good general principle, it is important that the FDA be much more specific in setting standards for acceptable PMTAs. Specifically, for all studies the applicant should be required to report the minimum detectable effect with 95% power for the sample sizes used in the applicant's studies. In addition, the FDA should require specific justification from the applicant as to why this minimum detectable effect size is APPH.

Proposed rule section 1114.7(k)(3)(v) requiring applicants to include a statistical analysis plan for the full report of each study included in the PMTA should be amended[45] to require presentation of such

[41] See Appendix, section 1114.33.
[42] See Appendix, section 1114.7(k)(1).
[43] Proposed rule, 84 FR at p. 50643.
[44] Proposed rule, 84 FR at p. 50650.
[45] See Appendix, section 1114.7(k)(3)(v).

power data, including study power and minimum detectable effect size as part of the statistical methods employed for analyzing the data in all studies.

Expecting studies to achieve 95% power is higher than the commonly used standard of 80% power when designing studies. The difference between most studies and those that are likely to be relevant in a PMTA application is that in most cases, studies are designed in hopes of rejecting the null hypothesis in detecting an effect, whereas in a PMTA, it may be in the interests of the applicant to fail to reject the null hypothesis, i.e., conclude that there is no effect. Because reaching a conclusion with high confidence of the lack of an effect is often likely to be key to a decision that a product is APPH, it is appropriate to require that such a negative conclusion be reached with 95% confidence, just as one usually seeks at least 95% confidence in rejecting the null hypothesis and concluding a positive effect.

FDA should not give undue emphasis to chemicals on the "harmful or potentially harmful constituents" (HPHC) list

The current HPHC list is heavily weighted toward carcinogens and based on important toxic chemicals in the cigarette. Many new tobacco products have exposure profiles that may deliver lower levels of some toxins on the current HPHC list, but which deliver substantially higher exposures to other toxins.[46] Thus, overemphasizing the HPHC list could lead to products that are not appropriate for the protection of public health because the FDA did **not** devote adequate attention to these other toxins. The FDA's proposal to expand the HPHC list addresses this problem to some extent, but it still leaves out important potential toxicants.[47]

Because of the intrinsic limitations of the HPHC list, a statement about the toxic constituents contained in the tobacco product that are not included in the current HPHC list should also be required to be submitted under proposed rule section 1114.7(i)(1)(v). While the HPHC list should be addressed, it should not be the "focus" of the toxicological assessment (as FDA stated[48] in the preamble). Proposed rule section 1114.7(i)(1)(v) should be amended[49] to clarify this.

As noted above, FDA approved Philip Morris' PMTA application for IQOS because exposure levels for several HPHCs were lower than a cigarette, despite the fact that Philip Morris's own data did not show

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[46] St.Helen G, Jacob III P, Nardone N, et al. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control 2018;27(Suppl 1):s30-s36;
St.Helen G, Jacob P III, Nardone N, Benowitz NL 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. Docket Number: FDA-2017-D-3001. November 29, 2017. Tracking number:1k1-902j-m8kv. https://www.regulations.gov/document?D=FDA-2017-D-3001-0129.

[47] Lempert LK, St.Helen G, Gotts J, et al. In addition to the 19 constituents FDA proposes to add to the list of Harmful and Potentially Harmful Constituents, FDA should also add compounds that may be carcinogenic or cause pulmonary or cardiovascular harms when inhaled, especially oils and chemicals and chemical classes found in e-cigarette flavorants, and FDA should use as additional criteria California's Proposition 65 list of carcinogens and reproductive toxicants and the California Air Resources Board's list of Toxicant Air Contaminants. Docket Number: FDA-2012-N-0143. October 2, 2019. Tracking Number: 1k3-9cij-8wgr.
https://www.regulations.gov/document?D=FDA-2012-N-0143-0037

[48] Proposed rule, 84 FR at p. 50601.

[49] See Appendix, section 1114.7(i)(1)(v).

any clinical or biological benefit for IQOS. ***FDA should make it clear in the final regulation that while the HPHCs and measures of exposure are important benchmarks to consider, the exposure assessment needs to cover the full range of exposures generated by the new product. FDA should also revise the final regulation to clearly state that evidence of biological and clinical effects of the product will be given more weight than measures of exposure.***

To this end, proposed rule §1114.27(b)(1)(ii) appropriately provides that "FDA intends to refuse to file a PMTA that does not include sufficient information about the product's health risks and a comparison of its health risks to other tobacco products on the market. FDA correctly stated,[50] "Information about the product's toxicity and a comparison of its toxicity to other tobacco products could satisfy this threshold information requirement for filing; however it should be noted that *information from nonclinical studies alone, including a products toxicological profile, is generally not sufficient to support a determination that permitting the marketing of the product would be APPH*. … If an application does not contain sufficient information about the health risks of the new tobacco product to allow FDA to make a determination regarding the potential risks and benefits of the population as a whole under section 910(c)(4) of the FD&C Act, FDA will issue a no marketing order for the new tobacco product [emphasis added]."

Moreover, the more critical thing for the FDA to consider is biological and clinical *effects* of exposure, not simply the *level* of exposure because many biological effects have nonlinear dose-response relationships in which substantial adverse effects occur at low doses. This is well-established in terms of cardiovascular endpoints and increasingly appears to be the case for pulmonary endpoints. There is even some evidence that cancer effects also exhibit nonlinear dose-response relationships.[51] **Rather than urging applicants to identify threshold levels for non-carcinogenic effects,[52] FDA should be directing applicants to give particular concern to nonlinear dose-response effects in which there are substantial effects at low levels of exposure.**

Proposed rule section 1114.7(i)(1)(v) should be amended[53] to change "other constituents" to "other constituents that may be substantial or have substantial health effects."

FDA should prioritize evidence about real-world actual use over clinical trials or laboratory studies

When discussing the kind of evidence required to provide the FDA to assess abuse liability, the FDA points out that "[t]he 'standard' abuse liability study is a double-blind, placebo-controlled, within-subject study comparing several doses of a new product to a comparator product with a known abuse liability."[54] Later the FDA goes on to state, "Real world, actual use data *may* also provide outcomes relevant to the products' abuse liability, including misuse [emphasis added]." This statement is weakened by including the word "may," and the proposed rule section 1114.7(k)(1)(ii)(A) should be amended to require applicants to submit real world, actual use data known or available to the applicant.[55]

For example, clinical trials generally show that e-cigarettes are effective devices to promote combustible cigarettes cessation, whereas real-world experience shows that e-cigarettes are associated with

[50] Proposed rule, 84 FR at p. 50602.
[51] Madison MC, Landers CT, Gu BH, et al., Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest. 2019 Sep 4. pii: 128531. doi: 10.1172/JCI128531. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31483291
[52] Proposed rule, 84 FR at p. 50601.
[53] See Appendix, section 1114.7(i)(1)(v).
[54] Proposed rule, 84 FR at p. 50604.
[55] See Appendix, 1114.7(k)(1)(ii)(A).

less quitting or have no significant effect on quitting.[56] These differences are due to the fundamentally different situations that exist in a laboratory study compared to real-world use including, as the FDA later points out, the fact that users may not use the product precisely as intended.

In the preamble to the proposed rule, FDA describes[57] the kind of "valid" scientific evidence that it intends to consider when assessing a proposed new product. These traditional scientific studies are an important source of information that are appropriately included in the regulation. The FDA statement that "isolated case reports, anecdotal experiences, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not considered valid scientific evidence" is appropriate. The one possible exception to this policy would be case reports published in the peer-reviewed literature that could provide early warning of adverse health effects in actual use. The FDA also appropriately states that "information from nonclinical studies alone is generally not sufficient to support a determination that permitting the marketing of the product would be APPH."

While the kind of laboratory studies that the FDA mentions are necessary to assess the biological likelihood of abuse liability, real-world studies are much more important for assessing whether a proposed new product is APPH. For this reason, proposed rule section 1114.7(k)(1) should be amended[58] to emphasize that health risk investigations in PMTAs must include evidence based on actual use in the real world.

Software

Proposed rule section 1114.7(i)(1)(i)[59] appropriately requires applicants to provide detailed information on any communications capacity or software embedded in a new tobacco product. The fact that electronic nicotine delivery systems are digital and hence subject to much finer control and possible feedback between user use and device characteristics is extremely dangerous. Such feedback could be made even more dangerous by allowing two-way communications between the device and a tobacco company or third party that can be used to adjust the device in a way that would increase consumption and addictive potential.[60]

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[56] Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med. 2016 Feb;4(2):116-28. doi: 10.1016/S2213-2600(15)00521-4. Epub 2016 Jan 14.

[57] Proposed rule, 84 FR at p. 50619.

[58] See Appendix, section 1114.7(k)(1).

[59] Proposed rule, 84 FR at p. 50644.

[60] Lempert LK, Glantz SA. Heated tobacco product regulation under US law and the FCTC. Tobacco Control 2018;27:s118-s125;
Lasseter T, Wilson D, Wilson T, *et al.*, May 15, 2018. Special Report: Philip Morris device knows a lot about your smoking habit. https://www.reuters.com/article/us-tobacco-iqos-device-specialreport/special-report-philip-morris-device-knows-a-lot-about-your-smoking-habit-idUSKCN1IG1IY;
Connolly GN. A Reduced Risk Nicotine Delivery Device or a Device to Enhance and Control Abuse (Addiction) Potential through Manipulation of the Pattern of Nicotine Delivery? https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM594333.pdf;
FDA, 2018. TPSAC Meeting Materials and Information, January 24-25, 2018: Transcript Day 1. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM599234.pdf;
FDA, 2018. TPSAC Meeting Materials and Information, January 24-25, 2018: Transcript Day 2.

For the same reason, proposed rule section 1114.7(i)(1)(i) appropriately requires applicants to provide a description of the software or technology, the purposed of the software or technology, and a description of the data collected by the software and how it will be used because these aspects of a product's software or technology could result in more frequent or intense use compared to currently marketed products. Proposed rule section 1114.7(i)(1)(i)[61] and section 1114.15(a)[62] should be amended to specifically require applicants to report in the PMTA and/or in any supplemental PMTA application any changes to the software or device that could result in two-way communication with the device or reprogramming of the nicotine delivery pattern (whether automatic or as the result of two-way communication with the device).

Product software details should be added to the required lists of "Product properties" for ENDS in Table 1[63] and to the list of "required design parameter information for ENDS" in Table 19.[64]

FDA should issue a no marketing order if the application does not include specific assurances supported by evidence that there will be no communication between the device and any external source, and that nothing in the software intrinsic to the device would be programmed to increase consumption. Proposed rule section 1114.33(a) should be amended[65] to reflect this.

Flavors in products

Proposed rule section 1114.7(c)(3)(iii) requires applicants to specify product properties, including "characterizing flavor," as provided in Table 1 to section 1114.7(c)(3)(iii). ***FDA should require disclosure of all flavoring agents (whether "characterizing" flavors or not) in all new tobacco products.*** The proposed rule and accompanying table should be amended[66] to reflect this important change.

Effects of new products on youth

***Proposed rule section 1114.7(k)(1)(i)[67] appropriately requires applications to contain full reports of all information, including both favorable and unfavorable, published or known to or which should reasonably be known to, the applicant concerning the potential health risks of the product to nonusers, including youth, and proposed rule section 1114.7(k)(1)(iii)(A)[68] appropriately requires applications to report all information on the potential impact the tobacco product and its labeling and advertising may have on tobacco use initiation by nonusers, particularly* youth and young adults.** Additionally, proposed rule section appropriately 1114.27(b)(1)[69] emphasizes the importance of this information by providing that FDA may refuse to file a PMTA if it does not contain a threshold amount of the information required by these sections. Further, FDA correctly states that "the advertising, marketing, and promotion of a tobacco product can have a significant impact on the potential for tobacco product initiation, especially by youth," and therefore "where FDA is unable to determine the impact that the labeling advertising, marketing, and promotion of the new tobacco product may have on consumer perceptions and use intentions, FDA intends

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https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM599235.pdf

[61] See Appendix, section 1114.7(i)(1)(i).

[62] See Appendix, section 1114.15(a).

[63] See Appendix, Table 1.

[64] See Appendix, Table 19.

[65] See Appendix, section 1114.33(a).

[66] See Appendix, section 1114.7(c)(3)(iii) and accompanying table.

[67] Proposed rule, 84 FR at p. 50650.

[68] Proposed rule, 84 FR at p. 50651.

[69] Proposed rule, 84 FR at p. 50655.

to issue a no marketing order [under proposed rule 1114.33] for the new tobacco product."[70] Proposed rule section 1114.33 should be amended[71] to explicitly include this factor.

When evaluating PMTAs, the FDA must consider data on youth (ages 12-25). This review must consider data on real and possible youth usage of the proposed new product, as well as perceptions of the product, product risk, and proposed marketing. In particular, the FDA must require from the applicant manufacturer reliable, scientific evidence on the impact of a product, its marketing, and its promotion on US youth, including: (1) attitudes and beliefs about the product and any claims made about it; (2) perceptions of the product's risk; (3) perceptions of product appeal; and (4) susceptibility and intentions to use. Such data are important to determine whether the product, as marketed, would encourage initiation among youth already using another tobacco product, as well as youth not otherwise using a tobacco product.

It is also important to emphasize that relying simply on post-market surveillance is not enough. We must have data on the likelihood of youth use and perceptions of the tobacco product and related marketing *before* the product comes to market, not after. Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them, the product's flavors, smell and taste, the product's perceived harm reduction, and the ease and location of use.[72] As a case in point, we learned post-market with e-cigarettes -- and especially Juul -- that youth were targeted and found the marketing, flavors, and the device themselves appealing.

One way to obtain information on adolescents' interests and behavior is to conduct studies with adolescents. Certainly, the idea is not that anyone would provide youth with a tobacco product and conduct randomized controlled studies or other studies on youth use. But there are ethical studies that can be done with youth, such as survey studies in which youth are provided with a picture of the new product and/or a description of the product, and youth are asked about their perceptions of the product, or asked to interpret marketing statements that are proposed by the company. For example, in a recent study of Philip Morris International's proposed marketing for IQOS, youth were randomly assigned to see either a "reduced exposure," "reduced risk," or neither claim. Perceptions of IQOS-related health risks and general harm and understanding of the term "switching completely" as used in PMI's proposed claims were compared. Results showed that youth exposed to either claim perceived lower risk than controls, and that 30% of the youth didn't understand the term "switching completely."[73] In a study[74] of California youth and young adults (mean age 17.5, SD = 1.7), participants were asked to indicate whether eight different ads for flavored e-cigarette products, randomly displayed, target someone younger than them, their age, someone a little older, or someone much older like their parents. Participants felt the ads were for someone just a little older than them (age 18 – 26; not for someone much older). More than half of participants felt ads for *cherry*, *vanilla cupcake*, *caramel,* and *smoothie* flavors were for someone their age. Ads were also seen as targeting an audience younger than them. Finally, survey-based studies and qualitative studies have assessed youth's understanding and perceptions of different tobacco products, showing that youth often harbor

[70] Proposed rule, 84 FR at p. 50606.
[71] See Appendix, section 1114.33.
[72] McKelvey, K., Ramos, M., Roditis, M., Ramamurthi, D., Halpern-Felsher, B. A Qualitative Analysis of Adolescents' Appeal of Various Tobacco Products. In preparation.
[73] McKelvey, K., Baiocchi, M., Halpern-Felsher, B. PMI's Heated Tobacco Products Marketing Claims of Reduced Risk and Reduced Exposure may Entice Youth to Try and Continue Using These Products. Tobacco Control. In press.
[74] McKelvey, K., Baiocchi, M., Ramamurthi, D., McLaughlin, S., Halpern-Felsher, B. Youth say ads for flavored e-liquids are for them. *Addictive Behaviors*. 2019 Apr;91:164-170. PMID:30314868.

misperceptions about these new products.[75,76,77]

Similar studies must be conducted on all other proposed new products, before a product comes to market, and all findings, regardless of direction of results, along with the sampling plan, analytic plan, tables, and conclusions, must be submitted for review. Other specific methods of conducting research with youth have been outlined in the IOM report on modified risk tobacco products.[78]

Of importance, however, is that no tobacco company should be permitted to conduct research on youth below the legal age for tobacco use (21, to be conservative) because they could use such information to design marketing campaigns to attract youth to their products. Instead, tobacco companies can examine adolescents' interest and behavior by examining existing research on other, similar products, such as electronic cigarettes, conducted with no direct or indirect involvement of tobacco companies or their agents.[79] For example, the experience with e-cigarettes, which have also been promoted with harm reduction and "smokeless" messages, is directly relevant to adolescents' likely reaction to other new tobacco products.

Information about the effects of advertising on youth should not be limited to the product under the PMTA, but also include the effect of the PMTA product advertising on perceptions of other tobacco products, particularly cigarettes. Nonsmoking youth who viewed e-cigarette advertising had reduced harm perceptions of cigarettes.[80]

Submission of Marketing Plans

Proposed rule section 1114.7(f)(2)[81] requires PMTAs to contain a description of the applicant's marketing plans (including plans for "labeling, advertising, marketing, promotion, and other consumer-directed activities regarding the new tobacco product") to help FDA understand and prevent or minimize the potential harm that could be caused by the marketing of a new tobacco product. "Consistent with its mission to protect the public health, FDA seeks to limit youth exposure to the labeling, advertising, marketing, or promotion of a new tobacco product in order to limit uptake of the new tobacco product by nonusers of the tobacco products, especially youth.

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[75] McKelvey, K., Baiocchi, M., Halpern-Felsher, B. Adolescents' and young adults' use and perceptions of pod-based electronic cigarettes. *JAMA Netw Open. 2018 Oct 05;1(6):e183535*. PMID:30646249.

[76] Roditis, M.L., & Halpern-Felsher, BL. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85. PMID: 26115908.

[77] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, BL. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66. PMID: 27107909.

[78] Institute of Medicine. 2012. *Scientific Standards for Studies on Modified Risk Tobacco Products*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294.

[79] Institute of Medicine. 2012. *Scientific Standards for Studies on Modified Risk Tobacco Products*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294.

[80] Kim, M.& Popova, L. & Halpern-Felsher, B. & Ling, P. (2017). Effects of E-Cigarette Advertisements on Adolescents' Perceptions of Tobacco Cigarettes. Health Communication. Special issue: Communication research about tobacco regulatory science.doi:10.1080/10410236.2017.1407230

[81] Proposed rule, 84 FR at p. 50643.

As FDA stated[82] in the preamble:

> FDA will also consider how the applicant intends to minimize the extent to which youth can access the product and are exposed to its marketing. Where FDA determines that restrictions on the sales and distribution of the new tobacco product (including access to, and the advertising and promotion of, the tobacco product) would be APPH, FDA can impose such restrictions under the terms of a marketing order as described in section VIII.D.

The proposed rule[81] appropriately requires each applicant's marketing plans to include, among other things, information describing the target adult audiences by age-range (including young adults ages 18-24) and other demographic or psychographic characteristics, any means to limit youth-access or youth-exposure to the products' labeling, advertising, marketing, or promotion, and, importantly "(v) The use of owned, earned, shared, or paid media to advertise or promote the products" and "(vi) The use of partners, sponsors, influencers, bloggers, or brand ambassadors to advertise or promote the products."

Additionally, proposed rule section 1114.41[83] requires each applicant that receives a marketing order to continue to report its marketing plans (including labeling, advertising, and promotion), and these periodic reports must include, among other requirements, a description of the implementation of such plans, including targeting of specific adult audiences by age-range (including young adults ages 18-24), actions taken to restrict youth-access and limit youth exposure to the products' labeling, advertising, marketing, or promotion, and the "Use of owned, earned, shared, or paid social media to create labeling for, advertise, market, or promote the products" and "an overall assessment of how the tobacco product continues to be appropriate for the protection of the public health."

The rule should also require the applicant to provide specific evidence that it can effectively age verify customers with government issued identification before allowing access to any websites or social media. The default position should be that it is, for all practical purposes, impossible to have meaningful age verification for any Internet sources.[84] A recent example of this can be found in the November 2019 State of California lawsuit against Juul Labs,[85] which alleges, among other things, that Juul Labs made online sales to consumers without properly verifying their identities.[86] In particular, the lawsuit describes in great detail how Juul Labs' age verification procedures were flawed in multiple respects, thereby "allowing hundreds of thousands of tobacco products to be sold and/or delivered to fictitious individuals at fictitious addresses," including to underage purchasers or to resellers who sold the products to underage consumers on the grey

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[82] Proposed rule, 84 FR at p. 50581.
[83] Proposed rule, 84 FR at pp. 50656-50657.
[84] Williams RS, Derrick J, Ribisl KM. Electronic cigarette sales to minors via the internet. JAMA Pediatrics. 2015;169(3):e1563;
Ribisl KM, Williams RS, Kim AE. Internet sales of cigarettes to minors. JAMA. 2003;290(10):1356–1359;
Williams RS, Ribisl KM, Feighery EC. Internet cigarette vendors' lack of compliance with a California state law designed to prevent tobacco sales to minors. Arch Pediatr Adolesc Med. 2006;160(9):988–989.
Jensen JA, Hickman NJ, III, Landrine H, Klonoff EA. Availability of tobacco to youth via the Internet. JAMA. 2004;291(15):1837;
King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among US middle and high school students. J Adolesc Health. 2014;54(1):40–46.
[85] The People of the State of California v. Juul Labs, Inc. et al., Complaint for Permanent Injunction, Abatement, Civil Penalties, and Other Equitable Relief. November 18, 2019. Available at: https://oag.ca.gov/news/press-releases/attorney-general-becerra-and-los-angeles-leaders-announce-lawsuit-against-juul
[86] California v. Juul at pp. 41-56.

market.[87] Juul Labs' so-called age-verification process claimed to confirm identity without considering customers' full addresses, which was "not merely a technical transgression, but a systemic procedural flaw with widespread consequences."[88] Additionally, Juul Labs was able to approve sales to underage consumers by encouraging them to alter their identifying information, and formulated its age verification process to "maximize the number of 'passes' rather than to minimize the number of underage sales."[89] ***The FDA should require, not recommend (as it did in the Philip Morris IQOS PMTA authorization and General Snus MRTP authorization), applicants to regularly report youth access to their online materials and include a trigger level of access that would automatically suspend any PMTA order.***

It is appropriate for FDA to require applicants to provide information about how they anticipate using social media and shared media to promote their products, and then later to periodically report how these plans were implemented. Unfortunately, it is impossible for all practical purposes to control or police such activities once they have been unleashed on the Internet. ***The use of partners, sponsors, influencers, bloggers, or brand ambassadors to create labeling for, market, advertise or promote the tobacco product should simply be prohibited. Proposed rule section 1114.33 on issuance of a no marketing order and proposed rule section 1114.35 on withdrawal of a marketing order should be amended[90] to explicitly add provisions stating that FDA must not issue a marketing order if it has evidence either before or after the issuance of a marketing order that the applicant has used any of these marketing techniques.***

In its discussion of FDA's proposed requirement for submitting marketing plans, FDA states that it "must also assess potential uptake of the new tobacco product by current tobacco users who would have otherwise stopped using tobacco products and how use of the new tobacco product may affect poly use behaviors and subsequent tobacco use."[91] This important requirement warrants the emphasis FDA has described; however, proposed rule section 1114.7(f)(2) does not include explicit language about dual use. While much of the discussion about new tobacco products for possible harm reduction has concentrated on the idea of "switching" from combustible cigarettes to the new product, the reality is that most adult users become dual users. ***The possibility and health effects of dual use need to be given more emphasis throughout the application process.*** Section 1114.7(f)(2) should be amended[92] to explicitly require marketing plans to address potential dual use.

The preamble of the proposed rule states,[93] "At this time, FDA is not proposing to require the submission of advertising for application filing, except where used as stimuli in studies (*e.g.,* stimuli in perception studies)." This is a mistake. ***At least during the initial five-year period that a new product is permitted on the market, FDA should require preauthorization of all advertising and marketing materials, and proposed rule section 1114.31 concerning issuance of a marketing order should be amended by adding subsection (c) which would explicitly require this.***

Likewise, proposed rule section 1114.7(k)(1)(iv)[94] requires PMTAs to include full reports on the impact of the product and its labeling, and advertising on individuals' perception of the product, use intentions, and ability to understand the labeling and instructions for use. When discussing these perception

[87] California v. Juul at p. 43.
[88] California v. Juul at p. 44.
[89] California v. Juul at p. 51.
[90] See Appendix, sections 1114.33 and 1114.35.
[91] Proposed rule, 84 FR at pp. 50580-50581.
[92] See Appendix, section 1114.7(f)(2).
[93] Proposed rule, 84 FR at p. 50582.
[94] Proposed rule, 84 FR at p. 50651.

and use intention studies in the preamble, the FDA states[95] "if the advertising used as stimuli is not representative of the advertising an applicant intends to use in marketing the product, the applicant would be required to indicate whether and how the study findings are still relevant to the likely impact of product advertising on consumer tobacco product perceptions and use intentions." This is also a mistake because it leaves the door open for applicants to develop and implement advertising campaigns that bear little resemblance to those used to justify the PMTA in the first place.

Any PMTA marketing order should be limited to advertising that provides the same perceptions and stimuli as the materials used to justify the PMTA. Any PMTA order should specify that it would be automatically withdrawn should the applicant implement advertising campaigns or other marketing that is not consistent with the materials submitted to obtain the PMTA marketing order.

Proposed rule section 1114.31(b)(3)[96] provides that FDA may include as part of the marketing order a requirement to maintain records and submit postmarket reports on information about the product's "labeling, advertising, marketing, promotional materials, or marketing plans not previously submitted to FDA." The preamble to this provision explains[97] that this would allow FDA to require that an applicant "provide information on marketing and promotional materials not previously submitted to the FDA *at least 30 days before initial publication*, dissemination to consumers, or use and engaging or communicating with consumers of such materials. … These items provide information it is important to FDA's determination of whether the continued marketing of the new tobacco product would be APPH over there FDA must withdraw a marketing order under section 910(d)(1)(A) of the FD&C Act because the marketing of the new tobacco product is no longer APPH. Receiving this information in advance of its first use would allow FDA to ensure it can appropriately track and monitor the impact that [sic] the use of such information. FDA anticipates it would uses authority on a case-by-case basis, especially as it relates to novel tobacco products for which the body of knowledge is still growing [emphasis added]." ***This is an appropriate requirement. Any PMTA marketing order should include this provision together with a provision allowing FDA to halt the use of any new advertising materials on an interim basis while the FDA considers whether these materials are APPH.*** However, the proposed rule should be amended[98] to add the "at least 30 days before initial publication…" language quoted above that was omitted from the current version of the proposed rule.

Proposed rule section 1114.35[99] appropriately authorizes FDA to withdraw a marketing order for a new tobacco product if it is not APPH or if it determines that any postmarket requirement, including any statutory reporting requirement and/or any other requirement imposed by the marketing order, has not been met.

Environmental considerations

Proposed rule section 1114.7(g)[100] appropriately requires applicants to include an assessment of the environmental impacts of the new product, and FDA indicates in the preamble[101] (but not in the rule itself) that FDA would consider how the new product may present different disposal issues. Failure to include an adequate environmental assessment would be sufficient grounds for FDA to deny a PMTA application. Existing rule 21 CFR 1105.10(a)(10) provides that FDA must refuse to accept for review any PMTA that

[95] Proposed rule, 84 FR at p. 50610.
[96] Proposed rule, 84 FR at p. 50655.
[97] Proposed rule, 84 FR at p. 50620.
[98] See Appendix, section 1114.31(b)(3).
[99] Proposed rule, 84 FR at p. 50656.
[100] Proposed rule, 84 FR at p. 50643.
[101] Proposed rule, 84 FR at p. 50583.

does not include an environmental assessment or a valid claim of categorical exclusion, and proposed rule section 1114.27(a)(iv)[102] lists this as one of several factors FDA will consider in its initial review of the PMTA. FDA correctly notes that "the only categorical exclusion currently available [under 21 CFR 25.35] is for the substantial equivalence premarket pathway, *not for PMTAs*. [emphasis added]"[103] Because the substantial equivalence pathway requires a demonstration that a new tobacco product is nearly identical to a grandfathered "predicate" product that was already being marketed as of February 2007, this pathway is not available for most new tobacco products seeking marketing authorization such as e-cigarettes and heated tobacco products because there were no predicate products on the market as of February 2007.

This is an important provision that should be vigorously enforced particularly for electronic nicotine delivery systems that include battery and electronic components as well as plastics which can be significant environmental contaminants, especially when combined with nicotine residue.

FDA appropriately requires that all PMTAs include an assessment of the environmental impacts of proposed products on the human environment, including direct effects, indirect effects, and cumulative effects, to determine whether they would cause foreseeable significant negative environmental impacts. Environmental assessment should include analysis of the environmental impacts of the agricultural production of nicotine used in proposed products, and the impacts of product manufacturing, distribution, and consumption as well as the impacts of disposed product waste.

The environmental toxicity of tobacco products is well established.[104] Nicotine agricultural production and manufacturing have been shown to be highly toxic to the human environment.[105] Concerns have been raised about the environmental impacts of ENDS.[106] Recent research has shown that ENDS waste can contaminate the environment.[107] ENDS waste can include painted reusable and disposable aerosolizers, e-cigarette cartridges, LED lamps, coils, wicks, microprocessor circuit boards with lead, mercury other heavy metals, flammable lithium ion batteries, e-juice bottles, rubber gaskets and plastic components covered with e-liquid residues including nicotine, the neurotoxicity of which has been established in animal models,[108] carcinogenic flavorants,[109] vegetable glycerol, propylene glycol, and benzoic acid. Packaging can contain painted paper, plastic internal packaging and adhesive glues. When ENDS waste products are discarded and enter storm drains, they can travel into creeks, rivers, lakes, deltas, bays and ultimately into

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[102] Proposed rule, 84 FR at p. 50654.

[103] Proposed rule, 84 FR at p. 50582.

[104] Slaughter E, Gersberg RM, Watanabe K, Rudolph J, Stransky C, Novotny TE. Toxicity of cigarette butts, and their chemical components, to marine and freshwater fish. *Tob Control.* 2011;20 Suppl 1:i25-29. World Health Organization. *Tobacco and its environmental impact: an overview.* Geneva2017.

[105] World Health Organization. *Tobacco and its environmental impact: an overview.* Geneva2017. Novotny TE, Bialous SA, Burt L, et al. The environmental and health impacts of tobacco agriculture, cigarette manufacture and consumption. *Bull World Health Organ.* 2015;93(12):877-880.

[106] Hendlin YH. Alert: Public Health Implications of Electronic Cigarette Waste. *Am J Public Health.* 2018;108(11):1489-1490.

[107] Mock J, Hendlin YH. Notes from the Field: Environmental Contamination from E-cigarette, Cigarette, Cigar, and Cannabis Products at 12 High Schools - San Francisco Bay Area, 2018-2019. *MMWR Morb Mortal Wkly Rep.* 2019;68(40):897-899.

[108] England LJ, Aagaard K, Bloch M, et al. Developmental toxicity of nicotine: A transdisciplinary synthesis and implications for emerging tobacco products. *Neurosci Biobehav Rev.* 2017;72:176-189.

[109] Jabba SV, Jordt SE. Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. *JAMA Intern Med.* 2019.

oceans.[110] For example, the State of California's November 2019 lawsuit against Juul Labs alleges that because Juul pods contain nicotine, which is a "toxic substance which can be absorbed dermally and is 'fatal to humans in low doses'" under federal law and is "an acutely hazardous waste" under California state law, disposal of Juul pods is a public nuisance.[111] Additionally, disposal of electronic cigarettes such as Juul burdens public schools.[112]

Under National Environmental Policy Act of 1969 (NEPA) part 102(2)(E) and the Council on Environmental Quality (CEQ) Regulations Implementing NEPA (CEQ regulations) (42 U.S.C. 4332(2); 40 CFR part 1500 to 1508), FDA is required to assess the environmental impacts of any proposed Federal action to ascertain the environmental consequences of that action on the quality of the human environment.

In 40 CFR §1500.1 the purpose is stated, "The NEPA process is intended to help public officials make decisions that are based on understanding of environmental consequences, and take actions that protect, restore, and enhance the environment." Further in §1500.2 the policy is stated, "Federal agencies shall to the fullest extent possible: (b) Implement procedures to make the NEPA process more useful to decision makers and the public; … and to emphasize real environmental issues and alternatives." The regulation (40 CFR §1508.14) specifies that the human environment "shall be interpreted comprehensively to include the natural and physical environment and the relationship of people with that environment."

The analysis of the environmental effects of production and waste from ENDS and all other products FDA considers for PMTA approval, as specified in 40 CFR §1508.8, must include: "(a) Direct effects, which are caused by the action and occur at the same time and place. (b) Indirect effects, which are caused by the action and are later in time or farther removed in distance, but are still reasonably foreseeable… and related effects on air and water and other natural systems, including ecosystems. Effects and impacts as used in these regulations are synonymous. Effects includes ecological (such as the effects on natural resources and on the components, structures, and functioning of affected ecosystems), aesthetic, historic, cultural, economic, social, or health, whether direct, indirect, or cumulative. Effects may also include those resulting from actions which may have both beneficial and detrimental effects, even if on balance the agency believes that the effect will be beneficial."

Given that research has shown that the agricultural production of nicotine and manufacturing of nicotine-containing products has substantial environmental impacts,[113] and ENDS and waste from ENDS consumption have been found in the environment,[114] FDA is obligated to assess the *cumulative impact* of ENDS and all other products FDA considers for PMTA approval on the human environment. "Cumulative impact" is defined in 40 CFR §1508.7 as: "the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions

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[110] Eriksen M, Lebreton LC, Carson HS, et al. Plastic Pollution in the World's Oceans: More than 5 Trillion Plastic Pieces Weighing over 250,000 Tons Afloat at Sea. *PLoS One.* 2014;9(12):e111913.

[111] California v. Juul at pp. 67-69.

[112] California v. Juul at p. 38.

[113] World Health Organization. *Tobacco and its environmental impact: an overview.* Geneva2017. Novotny TE, Bialous SA, Burt L, et al. The environmental and health impacts of tobacco agriculture, cigarette manufacture and consumption. *Bull World Health Organ.* 2015;93(12):877-880.

[114] Mock J, Hendlin YH. Notes from the Field: Environmental Contamination from E-cigarette, Cigarette, Cigar, and Cannabis Products at 12 High Schools - San Francisco Bay Area, 2018-2019. *MMWR Morb Mortal Wkly Rep.* 2019;68(40):897-899.

regardless of what agency (Federal or non-Federal) or person undertakes such other actions. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time."

The federal regulations require FDA to determine whether ENDS and all other products FDA considers for PMTA approval are likely to produce any foreseeable impact on the human environment that is *significant.* 40 CFR §1508.27 provides that "significant" as used in NEPA "requires considerations of both context and intensity." In particular, "(a) Context. This means that the significance of an action must be analyzed in several contexts such as society as a whole (human, national), the affected region, the affected interests, and the locality…Both short- and long-term effects are relevant. (b) Intensity. This refers to the severity of impact. Responsible officials must bear in mind that more than one agency may make decisions about partial aspects of a major action. The following should be considered in evaluating intensity: … (2) The degree to which the proposed action affects public health or safety… (5) The degree to which the possible effects on the human environment are highly uncertain or involve unique or unknown risks. (6) The degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a future consideration. (7) Whether the action is related to other actions with individually insignificant but cumulatively significant impacts. Significance exists if it is reasonable to anticipate a cumulatively significant impact on the environment. Significance cannot be avoided by terming an action temporary or by breaking it down into small component parts. (8) The degree to which the action may adversely affect districts, sites, highways, structures, or objects listed in or eligible for listing in the National Register of Historic Places or may cause loss or destruction of significant scientific, cultural, or historical resources. (9) The degree to which the action may adversely affect an endangered or threatened species or its habitat that has been determined to be critical under the Endangered Species Act of 1973. (10) Whether the action threatens a violation of Federal, State, or local law or requirements imposed for the protection of the environment."

Storage and stability of products

Proposed rule section 1114.7(i)(2)(vi)[115] appropriately requires companies to provide information on storage and stability of products "that establishes the microbial and chemical stability of the product throughout the shelf life…" This requirement is important because products can change during storage, such as when the flavoring agents and e-cigarette liquids degrade or react with each other to increase the toxicity of the liquids. In the preamble,[116] however, FDA states that where no shelf life is indicated, an applicant "should provide details of stability over a specified amount of time, and justify why that time period is appropriate" and may rely, for example, on a "typical period of time" in which their product is sold to consumers. While "typical" is not formally defined, in this context it could be interpreted as the median storage duration, i.e., the length of time that half the product would remain in storage. Because this would mean that the other half will remain in storage for longer, the requirement for "typical" storage is inadequate because it would subject half the population to products stored for longer than the "typical" length of time. A better requirement to meet the legal requirement of the product being APPH would be to report the upper bound length of time the product should remain in storage, such as the upper 95% confidence interval for storage duration and demonstrate that there was not substantial product degradation over this time.

The applicant should also be required to provide detailed plans for monitoring products that have been in storage too long and for removing these products from the consumer-products stream in a timely

[115] Proposed rule, 84 FR at p. 50649.
[116] Proposed rule, 84 FR at p. 50596.

manner. Additionally, applicants should be required to provide regular postmarket reports to FDA on how much product has been removed because it was in storage for too long and how that product was disposed of. Proposed rule section 1114.7(i)(2)(vi) should be amended[117] to reflect these requirements. Because proposed rule section 1114.35[118] authorizes FDA to withdraw a marketing order if any postmarket requirement has not been met, the marketing order for any tobacco product that does not provide these postmarket reports concerning storage and stability should be withdrawn.

Principles of operation

Proposed rule section 1114.7(i)(3)(ii) appropriately requires applicants to report the length of time it takes for a user to consume a single unit of the product. For electronic nicotine delivery systems, the FDA should also require specification of software or other controls in the device to limit the intensity of use, including but not limited to minimum inter-puff interval and maximum number of puffs per hour that the device will deliver. The proposed rule should be amended[119] to reflect this change. One problem with current e-cigarettes is that, unlike conventional combusted cigarettes, there are no intrinsic limits to how close together puffs can be taken or obvious cues (such as finishing a conventional combusted cigarette) that give the user an easy indicator of how fast he or she is consuming nicotine. Products should have limits on how close together puffs can be and how many puffs can be consumed per hour. These parameters should be set based on actual nicotine delivered to users in a way to minimize the nicotine abuse potential. ***In particular, devices should not be permitted to deliver nicotine more intensely or faster than in a conventional cigarette.***

Manufacturing

Proposed rule section 1114.7(j)[120] appropriately requires manufacturers to provide plans on how they would identify nonconforming products, such as those containing foreign objects or other non-tobacco-related materials. In issuing a marketing order, FDA should set a threshold for such problems that, if not met, would trigger an automatic suspension of that order.

FDA should submit PMTA applications to TPSAC so that they can be made available for public comment

While FDA is not required to make PMTA applications public, it does have the option under Tobacco Control Act section 910(b)(2) to submit them to TPSAC for review. Doing so would also make the applications available for public comment, which could be considered by both TPSAC and the FDA when making the final decision as to whether or not the proposed product is APPH. Proposed rule section 1114.27(c)(3) provides that FDA "may" refer the PMTA or portions of the PMTA, upon its own initiative or applicant request, to TPSAC. FDA should amend[121] this section to require that all PMTAs are made publicly available. If it is unfeasible to require the submission of *all* PMTA applications to TPSAC, FDA should at least submit applications from the major tobacco companies and representative applications from the smaller companies. The proposed rule should be amended to reflect this.

FDA should amend proposed section 1114.47,[122] which deals with confidentiality of PMTA applications to routinely inform TPSAC of the existence of all PMTA applications so that the public may

[117] See Appendix, section 1114.7(i)(2)(vi).
[118] Proposed rule, 84 FR at p. 50656.
[119] See Appendix, section 1114.7(i)(3)(ii).
[120] Proposed rule, 84 FR at p. 50650.
[121] See Appendix, section 1114.27(c)(3).
[122] See Appendix, section 1114.47(b).

comment on the need for referring applications to TPSAC which would create the appropriate opportunity for public comment. Although FDA discusses that in some cases, "premature disclosure" of PMTAs "could result in a competitive advantage,"[123] in some cases, including for IQOS, if the applicant has also submitted a MRTP that is made publicly available per Tobacco Control Act section 911(e), this concern is irrelevant. ***Therefore, proposed section 1114.47 should also be amended to provide that FDA shall publicly disclose the existence of PMTAs for which the applicant has previously submitted a Modified Risk Tobacco Product (MRTP) application, or submits a MRTP application concurrently with the PMTA.***

FDA should include triggers in all PMTA orders that will automatically withdraw market authorization if these specific trigger points are reached

FDA requests comments on its interpretation of the APPH standards set forth in section 910(c) of the FD&C Act, including how it should apply the standard over time as the tobacco product marketplace and tobacco product use behaviors change. While it is impossible to anticipate every possible change, ***FDA should include trigger points on issues such as increased youth use of all tobacco products that, if violated, would automatically withdraw the PMTA. Such bright line conditions, included as requirements rather than recommendations, would act as a more substantial restraint on industry behavior than the kinds of recommendations that the FDA has included in the IQOS and General Snus marketing orders.***

Tobacco Control Act section 910(d)(1)(A) provides that FDA *shall* withdraw a marketing order if it finds that "the continued marketing of such tobacco product no longer is appropriate for the protection of the public health." Proposed rule section 1114.35(a)(1) provides that FDA "may" withdraw a marketing order for a new tobacco product if FDA determines that "any of the grounds for withdrawal under section 910(d)(1) [including if it is no longer APPH]." This rule should be amended[124] to reflect the mandatory language of section 910(d)(1)(A). In the preamble,[125] FDA states that it can withdraw a marketing order if, among other things:

> The marketing of a product may no longer be APPH in several situations, including, for example, where there are changes to tobacco product use behaviors that were not expected in FDA's assessment of the PMTA (e.g., more nonusers of tobacco products are initiating use with the product than expected and/or fewer users of potentially more harmful products are switching to the potentially less harmful new tobacco product). Another example is where studies conducted after the issuance of the marketing order show that the product presents greater risks to health than the FDA understood during application review and, as a result, the product likely has or will have a net negative impact on the health of the population as a whole.

This is an appropriate standard that should be integrated explicitly into any PMTA marketing orders for the use of trigger levels as discussed above. At the same time, the FDA should write a marketing order in a way that permits the consideration of other unexpected factors not specifically listed as trigger factors in a marketing order.

In particular, FDA should withdraw or temporarily suspend any marketing order if FDA learns from *any* source (including, but not limited to, required reports submitted by applicants pursuant to section 1114.41, information FDA obtains from its own research or from outside sources concerning adverse experiences associated with the tobacco product, information submitted to FDA's reporting portals, and information FDA receives from public health officials or other interested members of the public) that the tobacco product is impacting the health of youth and young adults, including increases in the percentage of

[123] Proposed rule, 84 FR at p. 50624.
[124] See Appendix, section 1114.35(a)(1).
[125] Proposed rule, 84 FR at p. 50621.

youth and young adults who report use of the tobacco product. The definition of "adverse experience" in proposed rule section 1114.3 should be amended[126] to explicitly include increased use by youth and/or young adults.

To this end, the protocol for issuing temporary suspensions of marketing orders as provided in proposed rule section 1114.37[127] should be explicitly integrated into all PMTA marketing orders.

The FDA should explicitly consider any public comments submitted in response to MRTP applications for the same new product that is the subject of the PMTA application

Proposed rule section 1114.7(b)(2)[128] sets out the procedures for applicants who are seeking a PMTA marketing order and also wish to submit a MRTP application, including requiring that these applications be appropriately cross-referenced. This is an appropriate requirement. The FDA should make it clear that, as a matter of routine policy for assessing PMTAs, it will consider public comments submitted in response to the MRTP application. The FDA's assessment of these public comments should be explicitly addressed in any PMTA marketing order.

FDA should require submission of information about any solvent used in ENDS, not just propylene glycol and vegetable glycerin

Table 1 to proposed rule section 1114.7(c)(iii)[129] should be amended appropriately to reflect this change.

Conclusions

FDA's proposed rule for premarket tobacco product applications and recordkeeping requirements thoughtfully addresses the full range of issues that FDA should consider when reviewing PMTAs and determining whether permitting the marketing of the proposed new tobacco product would be "appropriate for the protection of the public health."

There are, however, several provisions that should be changed, strengthened, or clarified:

1) The rule should specifically require PMTAs to compare new tobacco products to *all* other tobacco products on the market, not just to combustible cigarettes.

2) Section 1114.33(a) should be amended to provide that FDA will issue a "no marketing order" if, after considering outside source of information during PMTA review, FDA finds that the new tobacco product is not appropriate for the protection of the public health. Because of the tobacco industry's well-documented history of conducting biased research or selectively citing self-serving studies, the rule appropriately requires PMTAs to provide a comprehensive assessment of *all* the available literature related to a new product, including both favorable and unfavorable. FDA should specifically assess the weight given to industry results as compared with independent scientific research, and should explicitly consider bias in industry studies.

3) FDA should revise all of the PMTA requirements to give more prominence to heart and lung disease effects. In particular, proposed rule section 1114.7(k)(1)(i)(B) should be amended to require applicants to prioritize submission of information regarding the cardiovascular and respiratory effects of the new

[126] See Appendix, section 1114.3.
[127] Proposed rule, 84 FR at p. 50656.
[128] Proposed rule, 84 FR at p. 50637.
[129] See Appendix, section 1114.7(c)(iii).

tobacco product, and additionally include effects on blood and intergenerational health effects caused by epigenetic changes.

4) Health effects studies submitted in support of PMTAs should specifically consider sensitive subpopulations.

5) FDA should require applicants to submit all marketing research related to the development of any proposed new product, specifically including research considering the positioning of the proposed new product as a competitor to quitting.

6) To assess the health impacts of dual use, proposed rule section 1114.7(k)(1)(i)(D) should be strengthened to require submission of meaningful estimates of true levels of dual and poly use based on research for the proposed product or comparable products.

7) Proposed rule section 1114.33 should be revised to explicitly include dual use and deterrence of complete quitting of all tobacco products as factors that FDA explicitly must consider when deciding whether to issue a "no marketing order."

8) FDA should require applicants to report information about use of newly deemed products that have been on the market prior to the deadline for submitting a PMTA.

9) FDA should require that all studies submitted in support of a PMTA be adequately powered, and proposed rule section 1114.7(k)(3)(v) should be amended to require presentation of power data, including study power and minimum detectable effect size, as part of the statistical methods used.

10) While consideration of FDA's list of harmful and potentially harmful constituents (HPHCs) are important, FDA should not give undue emphasis to the HPHC list. Rather, an application's exposure assessment should cover the full range of exposures generated by the new product. Additionally, FDA should revise the rule to clearly state that evidence of biological and clinical effects of the product will be given more weight than measures of exposure.

11) FDA should prioritize evidence about real-world actual use over clinical trials or laboratory studies. Therefore, proposed rule section 1114.7(k)(1) should be amended to emphasize that health risk investigations in PMTAs must include evidence based on actual use in the real world.

12) Proposed rule section 1114.33(a) should be amended to provide that FDA should issue a no marketing order if the application does not include specific assurances and evidence that there will be no communication between the device and any external source, and that the software would not be programmed to increase consumption.

13) Proposed rule section 1114.7(c)(3)(iii) should be amended to require disclosure of all flavoring agents (whether "characterizing" flavors or not) in all new tobacco products.

14) Proposed rule section 1114.7(k)(1)(i) appropriately requires applicants to submit all information, both favorable and unfavorable, on the potential health risks of the new product on youth and young adults. This information should include scientific evidence on the impact of a product's marketing and promotion on youth, including perceptions of the product's risk and appeal, and susceptibility and intentions to use. However, tobacco companies should not be permitted to conduct research on youth

below the legal age because they could use such information to design their marketing campaigns to attract youth.

15) Proposed rule section 1114.7(f)(2) appropriately requires PMTAs to contain descriptions of the applicant's marketing plans, including information describing the targeted audiences by age range, and to continue to report its marketing plans after receiving a marketing order. The rule should be amended to require age verification for all websites and social media, and should prohibit the use of partners, sponsors, influencers, bloggers, or rand ambassadors to market or promote the product.

16) Proposed rule section 1114.7(g) appropriately requires applicants to include an environmental assessment of the new product. The rule should be amended to specifically require information on the environmental impact of disposal of the product.

17) Proposed rule section 1114.7(i)(2)(vi) appropriately requires companies to provide information on storage and stability of products. The rule should be amended to additionally require applicants to provide regular postmarket reports on how much product has been removed because it was in storage for too long and how that product was dispose of.

18) Proposed rule section 1114.27(c)(3) should be amended to require FDA to make all PMTAs publicly available.

19) FDA should include triggers in all marketing orders issued upon review of PMTAs that will automatically withdraw marketing authorization if these specific trigger points are reached.

20) FDA should explicitly consider any public comments submitted in response to MRTP applications for the same new product that is the subject of the PMTA.

The specific wording changes are indicated in the Appendix below.

APPENDIX

Suggested amendments to proposed rule on premarket tobacco product applications

Additions are in ***bold italics*** and deletions are in ~~strikeout~~.

PART 1114--PREMARKET TOBACCO PRODUCT APPLICATIONS

Subpart A--General Provisions

Sec.

Authority: 21 U.S.C. 371, 374, 387a, 387i, and 387j.

Subpart A--General Provisions

§ 1114.1 Scope.

(a) This part sets forth the procedures and requirements for submitting a premarket tobacco product application (PMTA), the general procedures FDA will follow when evaluating a PMTA, and postmarket reporting requirements.

(b) This part does not apply to modified risk tobacco product applications, except that single applications under section 911(l)(4) of the Federal Food, Drug, and Cosmetic Act seeking both a marketing order under section 910(c) of the Federal Food, Drug, and Cosmetic Act and an order under section 911(g) of the Federal Food, Drug, and Cosmetic Act must satisfy the requirements of this part in addition to the requirements of section 911 of the Federal Food, Drug, and Cosmetic Act.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 1114.3 Definitions.

For purposes of this part:

Accessory means any product that is intended or reasonably expected to be used with or for the human consumption of a tobacco product; does not contain tobacco and is not made or derived from tobacco; and meets either of the following:

(1) Is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product; or

(2) Is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product, but:

(i) Solely controls moisture and/or temperature of a stored tobacco product; or

(ii) Solely provides an external heat source to initiate but not maintain combustion of a tobacco product.

Additive means any substance the intended use of which results or may reasonably be

expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substances intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding), except that such term does not include tobacco, or a pesticide chemical residue in or on raw tobacco or a pesticide chemical.

Adverse experience means any unfavorable physical or psychological effect in ~~a~~ ***one or more persons, including an increase in the percentage of youth and/or young adults who use the tobacco product,*** that is temporally associated with the use of or exposure to a tobacco product, whether or not the person uses the tobacco product, and whether or not the effect is considered to be related to the use of or exposure to the tobacco product.

Applicant means any person that submits a premarket tobacco product application to receive a marketing order for a new tobacco product.

Brand means a variety of tobacco product distinguished by the tobacco used, tar content, nicotine content, flavoring used, size, filtration, packaging, logo, registered trademark, brand name(s), identifiable pattern of colors, or any combination of such attributes.

Characteristics means the materials, ingredients, design, composition, heating source, or other features of a tobacco product.

Component or *part* means

(1) Any software or assembly of materials intended or reasonably expected:

(i) To alter or affect the tobacco product's performance, composition, constituents, or characteristics; or

(ii) To be used with or for the human consumption of a tobacco product.

(2) Component or part excludes anything that is an accessory of a tobacco product.

Composition means the materials in a tobacco product, including ingredients, additives,

and biological organisms. The term includes the manner in which the materials, for example, ingredients, additives, and biological organisms, are arranged and integrated to produce a tobacco product.

Constituent means any chemical or chemical compound in a tobacco product or in tobacco smoke or emission that is or potentially is inhaled, ingested, or absorbed into the body.

Container closure system means any packaging materials that are a component or part of the tobacco product.

Design means the form and structure concerning, and the manner in which components or parts, ingredients, software, and materials are integrated to produce a tobacco product.

Finished tobacco product means a tobacco product, including all components and parts, sealed in final packaging (e.g., filters or filter tubes sold to consumers separately or as part of kits).

Harmful or potentially harmful constituent or *HPHC* means any chemical or chemical compound in a tobacco product or tobacco smoke or emission that:

(1) Is or potentially is inhaled, ingested, or absorbed into the body, including as an aerosol or any other emission; and

(2) Causes or has the potential to cause direct or indirect harm to users or nonusers of tobacco products.

Heating source means the source of energy used to burn or heat the tobacco product.

Ingredient means tobacco, substances, compounds, or additives contained within or added to the tobacco, paper, filter, or any other component or part of a tobacco product, including substances and compounds reasonably expected to be formed through a chemical reaction during tobacco product manufacturing.

Label means a display of written, printed, or graphic matter upon the immediate container

of any article.

Labeling means all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.

Line data means an analyzable dataset of observations for each individual study participant, laboratory animal, or test replicate.

Marketing order means the order described in section 910(c)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act stating that the new tobacco product may be introduced or delivered for introduction into interstate commerce.

Material means an assembly of ingredients. Materials are assembled to form the tobacco product or components or parts of a tobacco product.

New tobacco product means:

(1) Any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or

(2) Any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

No marketing order means the order described in section 910(c)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act stating that the product may not be introduced or delivered for introduction into interstate commerce.

Other features means any distinguishing qualities of a tobacco product similar to those specifically enumerated in section 910(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. Such other features include harmful and potentially harmful constituents and any other product characteristics that relate to the chemical, biological, and physical properties of the tobacco

product.

Package or *packaging* means a pack, box, carton, or container of any kind or, if no other container, any wrapping (including cellophane), in which a tobacco product is offered for sale, sold, or otherwise distributed to consumers.

Premarket tobacco product application or *PMTA* means the application described in section 910(b) of the Federal Food, Drug, and Cosmetic Act. This term includes the initial premarket tobacco product application and all subsequent amendments.

Serious adverse experience means an adverse experience that results in any of the following outcomes:

(1) Death;

(2) A life-threatening condition or illness;

(3) Inpatient hospitalization or prolongation of existing hospitalization;

(4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

(5) A congenital anomaly/birth defect; or

(6) Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Tobacco product means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term "tobacco product" does not mean an article that under the Federal Food, Drug, and Cosmetic Act is a drug (section 201(g)(1)), a device (section 201(h)), or a combination product (section 503(g)).

Tobacco product manufacturer means any person, including a repacker or relabeler, who:

(1) Manufactures, fabricates, assembles, processes, or labels a tobacco product, or

(2) Imports a finished tobacco product for sale or distribution in the United States.

Unexpected adverse experience means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

(1) The known or foreseeable risks of adverse experiences associated with the use or exposure to the tobacco product as described in the PMTA and other relevant sources of information, such as the product labeling and postmarket reports;

(2) The expected natural progression of any underlying disease, disorder, or condition of the persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or

(3) The results of nonclinical investigations.

Subpart B--Premarket Tobacco Product Applications

§ 1114.5 Application submission.

An applicant may submit a PMTA to demonstrate that a new tobacco product meets the requirements to receive a marketing order. A new tobacco product may not be introduced or delivered for introduction into interstate commerce under this part until FDA has issued a marketing order for the product.

§ 1114.7 Required content and format.

(a) *General*. The PMTA must contain sufficient information for FDA to determine whether any of the grounds for denial specified in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply. The application must contain the following sections:

(1) General information (as described in paragraph (c) of this section);

(2) Descriptive information (as described in paragraph (d) of this section);

(3) Product samples (as described in paragraph (e) of this section);

(4) Labeling (as described in paragraph (f) of this section);

(5) Statement of compliance with part 25 of this chapter (as described in paragraph (g) of this section);

(6) Summary (as described in paragraph (h) of this section);

(7) Product formulation (as described in paragraph (i) of this section);

(8) Manufacturing (as described in paragraph (j) of this section);

(9) Health risk investigations (as described in paragraph (k) of this section); and

(10) The effect on the population as a whole (as described in paragraph (l) of this section);

(11) Certification statement (as described in paragraph (m) of this section).

(b) *Format.* (1) The application must be submitted using the form(s) that FDA provides, contain a comprehensive index (i.e., a listing of files and data associated with those files) and table of contents, be well-organized and legible, and be written in English. Documents that have been translated from another language into English (e.g., original study documents written in a language other than English) must be accompanied by: the original language version of the document, signed a statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation. As described in § 1114.49, the applicant must submit the application and all information supporting the application in an electronic format that FDA can process, read, review, and archive, unless FDA has granted a waiver.

(2) An applicant may include content in a submission by cross-reference to a tobacco product master file or a pending modified risk tobacco product application for the same tobacco product. Applicants using a master file must provide documentation of their right of reference for the master file and clearly identify the specific content being incorporated into the PMTA submission. Except as provided for in §§ 1114.15 and 1114.17, FDA will not consider content included by cross-reference to other sources of information outside of the submission.

(c) *General information*. The applicant must, by using the form FDA provides, specify the following general information:

(1) Applicant name, address, and contact information;

(2) Authorized representative or U.S. agent (for a foreign applicant), including the name, address, and contact information;

(3) The following information to uniquely identify the product:

(i) Manufacturer;

(ii) Product name(s), including brand and subbrand (or other commercial name(s) used in commercial distribution); and

(iii) The product ~~category~~ ***name***~~, product subcategory,~~ and product properties as provided in the following table. ***In particular, all flavoring agents must be provided.*** If the product does not have a listed product property, such as ventilation or characterizing flavor, the application must state "none" for that property.

Table 1 to § 1114.7(c)(3)(iii)

[Columns for "Tobacco product category" and "Tobacco product subcategory" should be deleted. Applicants should be instructed to provide all the information under "product properties" that are relevant to the particular type of product.]

Tobacco product category:	Tobacco product subcategory:	Product properties:
(A) Cigarettes	*(1)* Combusted, Filtered	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes) --Length (e.g., 89 millimeters (mm), 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) --Ventilation (e.g., 0%, 10%, 25%)

		-- ~~Characterizing~~ ***All flavoring agents*** (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Combusted, Nonfiltered	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes) --Length (e.g., 89 mm, 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) -- Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Combusted, Bidi, and Other	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes) --Length (e.g., 89 mm, 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) --Ventilation (e.g., 0%, 10%, 25%) (if applicable) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Noncombusted (e.g., heated tobacco)	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes, 25 cigarettes) --Length (e.g., 89 mm, 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) --Ventilation (e.g., 0%, 10%, 25%) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Source of energy (e.g., charcoal, electrical heater) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Cigarette, Co-Package	For a new co-packaged tobacco product composed of multiple cigarette tobacco products, include, as applicable, all properties for each individual tobacco product, as identified above.
(B) Roll-Your-Own Tobacco Products	*(1)* Roll-Your-Own Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20 g, 40 grams (g)) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(2) Rolling Paper	--Package type (e.g., bag, box, booklet) --Product quantity (e.g., 200 papers) --Length (e.g., 79 mm, 100 mm, 110 mm) --Width (e.g., 45 mm, 60 mm, 78 mm) -- **All flavoring agents** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(3) Cigarette Tube, Filtered	--Package type (e.g., bag, box) --Product quantity (e.g., 100 tubes, 200 tubes) --Length (e.g., 89 mm, 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) --Ventilation (e.g., 0%, 10%, 25%) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Cigarette Tube, Nonfiltered	--Package type (e.g., bag, box) --Product quantity (e.g., 100 tubes, 200 tubes) --Length (e.g., 89 mm, 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Filter	--Package type (e.g., bag, box) --Product quantity (e.g., 100 filters, 200 filters) --Length (e.g., 8 mm, 12 mm) --Diameter (e.g., 6 mm, 8.1 mm) --Ventilation (e.g., 0%, 10%, 25%) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) Paper Tip	--Package type (e.g., bag, box) --Product quantity (e.g., 200 tips, 275 tips) --Length (e.g., 12 mm, 15 mm) --Width (e.g., 27 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(7) Roll-Your-Own, Co-Package	--For a new tobacco product composed of multiple roll-your-own tobacco products, include all applicable properties for each tobacco product (e.g., roll-your own tobacco, rolling paper, filtered cigarette tube, nonfiltered cigarette tube, filter, paper tip) as identified above --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(8) Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product

(C) Smokeless Tobacco Products	*(1)* Moist Snuff, Loose	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20 g, 30 g)

		--Tobacco cut size (e.g., 5 mm, 7 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Moist Snuff, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20 g) --Portion count (e.g., 15 pouches, 20 pieces) --Portion mass (e.g., 1.5 g/pouch, 2 g/piece) --Portion length (e.g., 15 mm, 20 mm) --Portion width (e.g., 10 mm, 15 mm) --Portion thickness (e.g., 5 mm, 7 mm) --Tobacco cut size (e.g., 5 mm, 7 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~(e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Snus, Loose	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20 g, 2 ounces) --Tobacco cut size (e.g., 5 mm, 7 mm) -- *All flavoring agents* ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Snus, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20 g) --Portion count (e.g., 15 pouches, 20 pieces) --Portion mass (e.g., 1.5 g/pouch, 2 g/piece) --Portion length (e.g., 15 mm, 20 mm) --Portion width (e.g., 10 mm, 15 mm) --Portion thickness (e.g., 5 mm, 7 mm) --Tobacco cut size (e.g., 5 mm, 7 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(5) Dry Snuff, Loose	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20 g, 2 ounces) --Tobacco cut size (e.g., 0.05 mm, 0.07 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify

		the tobacco product (if applicable)
	(6) Dry Snuff, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid --Product quantity (e.g., 22.5 g, 20 g) --Portion count (e.g., 15 pouches, 20 pieces) --Portion mass (e.g., 1.5 g/pouch, 2 g/piece) --Portion length (e.g., 10 mm, 15 mm) --Portion width (e.g., 5 mm, 8 mm) --Portion thickness (e.g., 3 mm, 4 mm) --Tobacco cut size (e.g., 5 mm, 7 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen)
	(7) Dissolvable	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20 g) --Product form (e.g., strip, tablet, stick) --Portion count (e.g., 15 sticks, 20 tablets) --Portion mass (e.g., 1.5 g/strip, 1.0 g/piece) --Portion length (e.g., 10 mm, 15 mm) --Portion width (e.g., 5 mm, 8 mm) --Portion thickness (e.g., 3 mm, 4 mm) --Tobacco cut size (e.g., 0.05 mm, 0.07 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(8) Chewing Tobacco, Loose	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20 g, 40 g) --Tobacco cut size (e.g., 0.05 mm, 0.07 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(9) Chewing Tobacco, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20 g) --Product form (e.g., plug, twist, portioned chewing tobacco) --Portion count (e.g., 1 plug, 3 twists, 10 bits) --Portion mass (e.g., 2 g/bit) --Portion length (e.g., 8 mm, 10 mm) --Portion width (e.g., 6 mm, 8 mm) --Portion thickness (e.g., 5 mm, 7 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify

		the tobacco product (if applicable)
	(10) Smokeless Co-Package	--For a new tobacco product composed of multiple smokeless tobacco products, include all applicable properties for each individual tobacco product as identified above --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(11) Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product
(D) ENDS (Electronic Nicotine Delivery System)	*(1)* E-Liquid, Open	--Package type (e.g., bottle, box) --Product quantity (e.g., 1 bottle, 5 bottles) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol, cherry, wintergreen) --E-liquid volume (e.g., 10 milliliter (ml)) --Nicotine concentration (e.g., 0, 0.2 mg/ml) --Propylene glycol/ vegetable glycerin (PG/VG) ratio***, and/or other solvents*** (e.g., N/A, 0/100, 50/50) --***Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) E-Liquid, Closed	--Package type (e.g., cartridge) --Product quantity (e.g., 1 cartridge, 5 cartridges) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol, cherry, wintergreen) --E-liquid volume (e.g., 10 ml) --Nicotine concentration (e.g., 0, 0.2 mg/ml) --PG/VG ***and/or other solvents*** ratio (e.g., N/A, 0/100, 50/50) --***Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(3) E-Cigarette, Closed	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 e-cigarette, 5 e-cigarettes) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol, cherry, wintergreen) --Length (e.g., 100 mm, 120 mm) --Diameter (e.g., 6 mm, 8 mm) --E-liquid volume (e.g., 2 ml, 5 ml) --Nicotine concentration (e.g., 0, 0.2 mg/ml) --PG/***VG and/or other solvents*** ratio (e.g., N/A, 0/100, 50/50) --Wattage (e.g., 100 W, 200 W) --Battery capacity (e.g., 100 mAh, 200 mAh) --***Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product
	(4) E-Cigarette, Open	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 e-cigarette, 5 e-cigarettes)

		-- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol, cherry, wintergreen) --Length (e.g., 100 mm, 120 mm) --Diameter (e.g., 8 mm, 14 mm) --E-liquid volume (e.g., 2 ml, 5 ml) --Wattage (e.g., 100 W, 200 W) --Battery capacity (e.g., 100 mAh, 200 mAh) ***--Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) ENDS Component	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 e-cigarette, 5 e-cigarettes) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol, cherry, wintergreen) ***--Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) ENDS Co-Package	--For a new tobacco product composed of multiple ENDS tobacco products, include all applicable properties for each individual tobacco product as identified above ***--Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(7) ENDS Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol) ***--Product software or technology (e.g., Bluetooth)*** --Additional properties needed to uniquely identify the tobacco product
(E) Cigars	*(1)* Cigar, Filtered Sheet-Wrapped	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 filtered cigars, 25 filtered cigars) -- ***All flavoring agents*** ~~Characterizing flavor~~ (e.g., none, menthol) --Length (e.g., 89 mm, 100 mm) --Diameter (e.g., 6 mm, 8.1 mm) --Ventilation (e.g., none, 10%, 25%) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(2) Cigar, Unfiltered Sheet-Wrapped	--Package type (e.g., box, film sleeve) --Product quantity (e.g., 1 cigar, 5 cigarillos) -- ***All flavoring agents*** ~~Characterizing flavor~~ (e.g., none, menthol) --Length (e.g., 100 mm, 140 mm) --Diameter (e.g., 8 mm, 10 mm) --Tip (e.g., none, wood tips, plastic tips) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Cigar, Leaf-Wrapped	--Package type (e.g., box, film, sleeve, none)

		--Product quantity (e.g., 1 cigar, 5 cigars) -- ***All flavoring agents*** ~~Characterizing flavor~~ (e.g., none, whiskey) --Length (e.g., 150 mm, 200 mm) --Diameter (e.g., 8 mm, 10 mm) -Wrapper material (e.g., burley tobacco leaf, Connecticut shade grown tobacco leaf) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Cigar Component	--Package type (e.g., box, booklet) --Product quantity (e.g., 10 wrappers, 20 leaves) -- ***All flavoring agents*** ~~Characterizing flavor~~ (e.g., none, menthol, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Cigar Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20 g, 16 ounces) -- ***All flavoring agents*** ~~Characterizing flavor~~ (e.g., none, menthol, cherry) --Tobacco cut size (e.g., 15 cuts per inch) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) Cigar Co-Package	--For a new tobacco product composed of multiple cigar tobacco products, include all applicable properties for each individual tobacco product as identified above --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(7) Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product
(F) Pipe Tobacco Products	*(1)* Pipe	--Package type (e.g., box, none) --Product quantity (e.g., 1 pipe) --Length (e.g., 200 mm, 300 mm) --Diameter (e.g., 25 mm) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~(e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Pipe Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20 g, 16 ounces) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, cavendish, cherry) --Additional properties needed to uniquely identify

		the tobacco product (if applicable)
	(3) Pipe Component	--Package type (e.g., bowl, shank, stem, screen, filter) --Product quantity (e.g., 1 bowl, 1 stem, 100 filters)

		-- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Pipe Co-Package	--For a new tobacco product composed of multiple pipe tobacco products, include all applicable properties for each individual tobacco product as identified above --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product
(G) Waterpipe Tobacco Products	*(1)* Waterpipe	--Package type (e.g., box, none) --Product quantity (e.g., 1 waterpipe) --Length (e.g., 200 mm, 500 mm) --Width (e.g., 100 mm, 300 mm) --Number of hoses (e.g., 1, 2, 4) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Waterpipe Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20 g, 16 ounces) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol, apple) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Waterpipe Heat Source	--Package type (e.g., box, film sleeve, bag, none) --Product quantity (e.g., 150 g, 680 g) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~(e.g., none, menthol, apple) --Portion count (e.g., 20 fingers, 10 discs, 1 base) --Portion mass (e.g., 15 g/finger) --Portion length (e.g., 40 mm, 100 mm) --Portion width (e.g., 10 mm, 40 mm) --Portion thickness (e.g., 10 mm, 40 mm) --Source of energy (e.g., charcoal, battery, electrical) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(4) Waterpipe Component	--Package type (e.g., bag, box, none) --Product quantity (e.g., 1 base, 1 bowl, 1 hose, 10 mouthpieces) -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, menthol, apple) --Additional properties needed to uniquely identify

		the tobacco product (if applicable)
	(5) Waterpipe Co-Package	--For a new tobacco product composed of multiple waterpipe tobacco products, include all applicable properties for each individual tobacco product as identified above --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) Waterpipe Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
Other	Other	--Package type (e.g., bag, box) --Product quantity -- ***All flavoring agents*** ~~Characterizing flavor(s)~~ (e.g., none, tobacco, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)

(4) The type of PMTA (i.e., PMTA, supplemental PMTA, or resubmission);

(5) Whether the applicant requests that FDA refer the PMTA to the Tobacco Products Scientific Advisory Committee (TPSAC);

(6) Identifying information regarding any prior submissions regarding the tobacco product (e.g., submissions related to investigational tobacco products, substantial equivalence reports, PMTAs), including submission tracking numbers (STNs) where applicable;

(7) Dates and purpose of any prior meetings with FDA regarding the new tobacco product;

(8) Address and the Facility Establishment Identifier (FEI) number(s), if available, of the establishment(s) involved in the manufacture of the new tobacco product;

(9) A brief statement regarding how the PMTA satisfies the content requirements of section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act;

(10) A brief description of how marketing of the new tobacco product would be appropriate for the protection of the public health; and

(11) A list identifying all enclosures, labels, and labeling being submitted with the application.

(d) *Descriptive information.* The application must contain descriptive information in this section that outlines the major aspects of the new tobacco product, including the following items:

(1) A concise description of the new tobacco product;

(2) A statement identifying all tobacco product standards issued under section 907 of the Federal Food, Drug, and Cosmetic Act that are applicable to the new tobacco product and a brief description of how the new tobacco product fully meets any identified tobacco product standard, or if the new tobacco product deviates from a product standard, if applicable, the application must include adequate information to identify and justify those deviations;

(3) The name(s) of the product as designated on the product's label;

(4) A description of problems that were identified in prototypes that are the subject of studies in the application and previous or similar versions of the new tobacco product that were marketed, if any. If there are previous or similar versions that are the subject of studies in the application or were marketed, the application must contain a bibliography of all reports regarding the previous or similar version of the product, whether adverse or supportive; and

(5) Any restrictions on the sale, distribution, advertising, or promotion of the new tobacco product that the applicant proposes to be included as part of a marketing order under section 910(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act to help support a showing that the marketing of the product is appropriate for the protection of the public health. If there are no proposed restrictions, the application must contain a statement to that effect.

(e) *Samples of new tobacco products*. After FDA accepts a PMTA for review, it may require the submission of samples of the new tobacco product, including its components and parts. If required, the applicant must submit samples of the finished tobacco product or its components or parts in accordance with instructions provided by FDA. FDA may also require the submission of additional samples to further aid in its review.

(f) *Labeling and marketing plans*--(1) *Labeling*. The application must contain specimens of all proposed labeling for the new tobacco product, including labels, inserts, onserts, instructions, and other accompanying information. The specimens of labeling must include all panels, reflect the actual size and color proposed to be used for the tobacco product, and include any warning label statements and other information required by regulation or statute, as applicable.

(2) *Marketing plans*. A PMTA must contain a description of the applicant's plans for labeling, advertising, marketing, promotion, and other consumer-directed activities regarding the new tobacco product developed by the time of filing. Such marketing plans must contain descriptions of actions that would be taken by the applicant, on behalf of the applicant, or at the applicant's direction for at least the first year the product would be marketed after receiving an order. If an applicant does not intend to use any advertising, marketing, promotion, or other communication activities directed at consumers, or has not developed marketing plans by the time of submission, the PMTA must contain a statement to that effect. As part of the description of the marketing plan, the PMTA must specify items such as the intended target audience(s), media and distribution channels, particular tactics, total dollar amount(s) of media buys and marketing and promotional activities (where applicable), and timing for the activities, including, but not limited to, information describing:

(i) The use of competent and reliable data sources, tools, technologies, and methodologies to establish, maintain, and monitor highly targeted marketing plans and media buys;

(ii) The target adult audiences by age-range(s) (including young adult audiences ages 18 to 24), and other demographic or psychographic characteristics;

(iii) The insights into the target audience the applicant is using to inform its marketing plans, including its strategic approach, key messages and themes, creative direction, and potential marketing tactics or channels;

(iv) The insights into how the product's planned labeling, marketing, advertising, and promotion affects potential uptake of the new tobacco product by current tobacco product users who would have otherwise stopped using tobacco products and how use of the new product may affect dual- and poly-use behaviors and subsequent tobacco use;

(v) Any means by which youth-access or youth-exposure to the products' labeling, advertising, marketing, and promotion would be limited;

(vi) The use of owned, earned, shared, or paid media to advertise or promote the products;

(vii) The use of partners, sponsors, influencers, bloggers, or brand ambassadors to advertise or promote the products;

(viii) The use of consumer engagements, including events at which the products will be demonstrated or sampled; and

(ix) The use of earned media, public-relations, or other communications outreach to promote the products.

(g) *Statement of compliance with 21 CFR part 25*. (1) The application must contain an environmental assessment prepared in accordance with § 25.40 of this chapter, or a valid claim of categorical exclusion, if applicable. If the applicant believes that the action qualifies for an

available categorical exclusion, the applicant must state under § 25.15(a) and (d) of this chapter that the action requested qualifies for a categorical exclusion, citing the particular exclusion that is claimed, and that to the applicant's knowledge, no extraordinary circumstances exist under § 25.21 of this chapter.

(2) Where the new tobacco product results from modifications to a legally marketed predecessor product, the environmental assessment must state whether the new tobacco product is intended to replace the predecessor tobacco product once the new tobacco product receives market authorization and is commercially marketed, be a line extension of the predecessor tobacco product, be marketed along with the predecessor product by the same manufacturer, or be marketed along with the predecessor tobacco product by a different manufacturer.

(h) *Summary*. The application must include a summary of all information contained in the application, including the following items, and identify areas in which there is a lack of information, where applicable:

(1) A summary of the product formulation section of the application;

(2) A summary of the manufacturing section of the application;

(3) A summary of the health risk investigations section of the application, including all information regarding:

(i) The health risks of the tobacco product to both users and nonusers of the product and whether the tobacco product may present less health risk than ***all*** other tobacco products;

(ii) The impact the product and its marketing will have on the likelihood of changes in tobacco use behavior, including cessation, of tobacco product users;

(iii) The impact the product and its marketing will have on the likelihood of tobacco use initiation by tobacco products nonusers;

(iv) How users and nonusers perceive the risk of the tobacco product based upon its

labeling, packaging, and marketing;

(v) Whether users are able to understand the labeling and instructions for use, and use the product in accordance with those instructions; and

(vi) The impact of human factors on the health risks to product users and nonusers (as described in paragraph (k)(1)(v) of this section);

(4) A concluding discussion describing how the data and information contained in the PMTA both constitute valid scientific evidence and establish that permitting marketing of the new tobacco product is appropriate for the protection of the public health, as determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product.

(i) *Product formulation*. The application must contain a full statement of the components or parts, materials, ingredients, additives, constituents, properties, and the principle or principles of operation, of the tobacco product, including the following information:

(1) *Components or parts, materials, ingredients, additives, and constituents*. The applicant must provide a full statement of:

(i) *Components or parts*. The quantity, function, and purpose of, and, where applicable, target specification(s) of, each component or part in the product. Where the tobacco product contains software components, the applicant must provide:

(A) A description of the software or technology (e.g., Bluetooth);

(B) The purpose of the software or technology, such as monitoring where tobacco products are located, activated, or used;

(C) A description of the data collected by the software and how it will be used;

(D) A description of how the software or technology may be used for two-way communication with the device and/or reprogramming of the nicotine delivery pattern (whether this reprogramming of the nicotine delivery pattern is automatic or as the result of two-way communication with the device).

(ii) *Materials*. For each material in the product, include:

(A) The material name and common name(s), if applicable;

(B) The component or part of the tobacco product where the material is located;

(C) The subcomponent or subpart where the material is located, if applicable;

(D) The function of the material;

(E) The quantities (including ranges or means and acceptance limits) of the material(s) in the new tobacco product;

(F) The specification(s) (including quality/grades and suppliers) used for the new tobacco product; and

(G) Any other material properties to fully characterize the new tobacco product.

(iii) *Ingredients other than tobacco*. For ingredients other than tobacco in each component or part of the product, include:

(A) The International Union of Pure and Applied Chemistry (IUPAC) chemical name and common name, if applicable;

(B) The Chemical Abstracts Service (CAS) number or FDA Unique Ingredient Identifier (UNII);

(C) The function of the ingredient;

(D) The quantity with the unit of measure (including ranges or means and acceptance limits) of the material(s) of the ingredients in the tobacco product reported as mass per gram of tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products;

(E) The specification(s) (including purity or grade and supplier); and

(F) For complex purchased ingredients, each single chemical substance reported

separately.

(iv) *Tobacco ingredients*. For tobacco ingredients in each component or part, include the following information or, if applicable, a statement that the product does not contain tobacco ingredients:

(A) The type(s), including grade(s) and variety/varieties;

(B) The quantity with the unit of measure (including ranges or means, acceptance limits) of tobacco in the tobacco product reported as mass per gram of tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products (with any specification variation, if applicable);

(C) The specification of tobacco used for the new tobacco product (with any specification variation, if applicable); and

(D) A description of any genetic engineering of the tobacco that impacts product characteristics.

(v) *Constituents*. ~~Constituents~~ ***All constituents***, including, ***but not limited to,*** HPHCs and other constituents ***that may be substantial or have substantial health effects***, contained within, or emitted from (including its smoke or aerosol), the product, including any reaction product from leaching or aging, by providing:

(A) The constituent names in alphabetical order;

(B) The common name(s);

(C) The Chemical Abstract Services number;

(D) The mean quantity and variance with unit of measure;

(E) The number of samples and measurement replicates for each sample;

(F) The analytical methods used and associated reference(s);

(G) The name and location of the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally recognized external accreditation organization;

(H) Length of time between dates of manufacture and date(s) of testing;

(I) Storage conditions of the tobacco product before it was tested; and

(J) Test data including test protocols, any deviation(s) from the test protocols, quantitative acceptance (pass/fail) criteria, and line data for all testing performed. Test data for combusted or inhaled products must reflect testing conducted using both intense and nonintense smoking regimens.

(vi) *Container closure system*. A description of the container closure system, including:

(A) Information describing how the container closure system protects and preserves the product from damage during transport, environmental contaminants, and potential leaching and migration of packaging constituents into the new tobacco product; and

(B) Information describing design features developed to prevent the risk of accidental exposure, if any.

(vii) *Statement of tobacco blending, reconstitution, or manipulation*. Information regarding tobacco blending, reconstitution, or manipulation, where applicable.

(2) *Other properties*. The applicant must provide a full description of the additional properties of the tobacco product that includes:

(i) *Product dimensions and construction*. The product dimensions and the overall construction of the product using a diagram or schematic drawing that clearly depicts the finished tobacco product and its components with dimensions, operating parameters, and materials.

(ii) *Design parameters and test data*. (A) All final design parameters of the product, specifying nominal values or the explicit range of values as well as the design tolerance (where appropriate), including, but not limited to, the parameters specified in tables 1 to 20 of this paragraph as applicable; and

(B) A quantitative description of the performance criteria, including test protocols, line data, and a summary of the results, for each applicable intermediate and final design parameter and manufacturing step, that includes, but is not limited to the test data specified in tables 1 to 20 of this paragraph for the product category as applicable:

Table 1 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Cigarettes

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigarette mass (mg) • Cigarette length (mm) • Cigarette diameter (mm) • Cigarette draw resistance (mm H_2O) • Tobacco rod length (mm) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (mm) • Tobacco moisture (%) • Cigarette paper length (mm) • Cigarette paper width (mm) • Cigarette paper base paper basis weight (g/m^2) • Cigarette paper base paper porosity (CU) • Cigarette paper band porosity (CU) • Cigarette paper band diffusivity (cm^2/s) • Cigarette paper band width (mm) • Cigarette paper band space (mm) • Filter length (mm) • Filter diameter (mm) • Filter mass (mg) • Filter density (g/cm^3) • Filter tow crimping index • Filter pressure drop (mm H_2O) • Filter efficiency (%)	• Cigarette mass (mg) • Cigarette length (mm) • Cigarette diameter(mm) • Cigarette draw resistance (mm H_2O) • Puff count • Tobacco rod length (mm) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (mm) • Tobacco moisture (%) • Cigarette paper length (mm) • Cigarette paper width (mm) • Cigarette paper base paper basis weight (g/m^2) • Cigarette paper base paper porosity (CU) • Cigarette paper band porosity (CU) • Cigarette paper band diffusivity (cm^2/s) • Cigarette paper band width (mm) • Cigarette paper band space (mm) • Filter length (mm) • Filter diameter (mm) • Filter mass (mg) • Filter density (g/cm^3) • Filter tow crimping index • Filter pressure drop (mm H_2O)

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Filter total denier (g/9000m) • Filter denier per filament (dpf) • Plug wrap length (mm) • Plug wrap width (mm) • Plug wrap basis weight (g/m^2) • Plug wrap porosity (CU) • Tipping paper length (mm) • Tipping paper width (mm) • Tipping paper basis weight (g/m^2) • Tipping paper perforation (CU) • Filter ventilation (%) • Filter ventilation position of holes • Filter ventilation number of holes • Filter ventilation number of rows	• Filter efficiency (%) • Filter total denier (g/9000m) • Filter denier per filament (dpf) • Plug wrap length (mm) • Plug wrap width (mm) • Plug wrap basis weight (g/m^2) • Plug wrap porosity (CU) • Tipping paper length (mm) • Tipping paper width (mm) • Tipping paper basis weight (g/m^2) • Tipping paper perforation (CU) • Filter ventilation (%)

Table 2 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Portioned and Nonportioned Smokeless Tobacco Products

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
Portioned Smokeless Tobacco Products	
• Tobacco cut size (mm) • Tobacco moisture (%) • Portion length (mm) • Portion width (mm) • Portion mass (mg) • Portion thickness (mm) • Pouch material basis weight (g/m^2) • Pouch material air permeability ($L/m^2/s$) • Pouch material nicotine dissolution rate (%/min) • Pouch material nicotine dissolution extent (mg) • Pouch material thickness (μm)	• Tobacco cut size (mm) • Tobacco moisture (%) • Portion length (mm) • Portion width (mm) • Portion mass (mg) • Portion thickness (mm) • Pouch material basis weight (g/m^2) • Pouch material air permeability ($L/m^2/s$) • Pouch material nicotine dissolution rate (%/min) • Pouch material nicotine dissolution extent (mg) • Pouch material thickness (μm)
Nonportioned Smokeless Tobacco Products	
• Tobacco cut size (mm) • Tobacco moisture (%)	• Tobacco cut size (mm) • Tobacco moisture (%)

Table 3 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Rolling Papers

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Roll-your-own (RYO) paper length (mm) • RYO paper width (mm) • RYO paper mass (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper base paper porosity (CU) • RYO paper band porosity (CU) • RYO paper band diffusivity (cm^2/s) • RYO paper band width (mm) • RYO paper band space (mm)	• RYO paper length (mm) • RYO paper width (mm) • RYO paper mass (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper base paper porosity (CU) • RYO paper band porosity (CU) • RYO paper band diffusivity (cm^2/s) • RYO paper band width (mm) • RYO paper band space (mm)

Table 4 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Tubes

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tube mass (mg) • Tube length (mm) • Tube diameter (mm) • Tube paper length (mm) • Tube paper width (mm) • Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (CU) • Tube paper band porosity (CU) • Tube paper band diffusivity (cm^2/s) • Tube paper band width (mm) • Tube paper band space (mm)	• Tube mass (mg) • Tube length (mm) • Tube diameter (mm) • Tube paper length (mm) • Tube paper width (mm) • Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (CU) • Tube paper band porosity (CU) • Tube paper band diffusivity (cm^2/s) • Tube paper band width (mm) • Tube paper band space (mm)

Table 5 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Filtered Tubes

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tube mass (mg) • Tube length (mm) • Tube diameter (mm) • Tube paper length (mm) • Nonfilter tube length (mm) • Tube paper width (mm)	• Tube mass (mg) • Tube length (mm) • Tube diameter (mm) • Tube paper length (mm) • Nonfilter tube length (mm) • Tube paper width (mm)

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (CU) • Tube paper band porosity (CU) • Tube paper band diffusivity (cm^2/s) • Tube paper band width (mm) • Tube paper band space (mm) • Filter length (mm) • Filter diameter (mm) • Filter mass (mg) • Filter density (g/cm^3) • Filter tow crimping index • Filter pressure drop (mm H_2O) • Filter efficiency (%) • Filter total denier (g/9000m) • Filter denier per filament (dpf) • Plug wrap length (mm) • Plug wrap width (mm) • Plug wrap basis weight (g/m^2) • Plug wrap porosity (CU) • Tipping paper length (mm) • Tipping paper width (mm) • Tipping paper basis weight (g/m^2) • Tipping paper perforation (CU) • Filter ventilation (%) • Filter ventilation position of holes • Filter ventilation number of holes • Filter ventilation number of rows	• Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (CU) • Tube paper band porosity (CU) • Tube paper band diffusivity (cm^2/s) • Tube paper band width (mm) • Tube paper band space (mm) • Filter length (mm) • Filter diameter (mm) • Filter mass (mg) • Filter density (g/cm^3) • Filter tow crimping index • Filter pressure drop (mm H_2O) • Filter efficiency (%) • Filter total denier (g/9000m) • Filter denier per filament (dpf) • Plug wrap length (mm) • Plug wrap width (mm) • Plug wrap basis weight (g/m^2) • Plug wrap porosity (CU) • Tipping paper length (mm) • Tipping paper width (mm) • Tipping paper basis weight (g/m^2) • Tipping paper perforation (CU) • Filter ventilation (%)

Table 6 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for RYO Tobacco

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco filler mass (mg) • Tobacco cut size (mm) • Tobacco moisture (%)	• Tobacco filler mass (mg) • Tobacco cut size (mm) • Tobacco moisture (%)

Table 7 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Paper Tips

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• RYO paper tip length (mm) • RYO paper tip width (mm) • RYO paper tip mass (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper perforation (CU) • RYO paper tip ventilation (%)	• RYO paper tip length (mm) • RYO paper tip width (mm) • RYO paper tip mass (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper perforation (CU) • RYO paper tip ventilation (%)

Table 8 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Filtered Sheet-Wrapped Cigars

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar length (mm) • Cigar diameter (mm) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (mm) • Tobacco moisture (%) • Cigar wrapper porosity (CU) • Cigar binder porosity (CU) • Filter length (mm) • Filter diameter (mm) • Filter pressure drop (mm H_2O) • Filter efficiency (%) • Tipping paper length (mm) • Filter ventilation (%)	• Cigar length (mm) • Cigar diameter (mm) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (mm) • Tobacco moisture (%) • Cigar wrapper porosity (CU) • Cigar binder porosity (CU) • Filter length (mm) • Filter diameter (mm) • Filter pressure drop (mm H_2O) • Filter efficiency (%) • Tipping paper length (mm) • Filter ventilation (%)

Table 9 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Unfiltered Sheet-Wrapped Cigars

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar mass (mg) • Cigar length (mm) • Cigar minimum diameter (mm) • Cigar maximum diameter (mm) • Tobacco filler mass (mg) • Cigar wrapper porosity (CU) • Cigar tip length (mm) (if applicable) • Cigar tip inner diameter (mm) (if applicable) • Cigar tip width (mm) (if applicable)	• Cigar mass (mg) • Cigar length (mm) • Cigar minimum diameter (mm) • Cigar maximum diameter (mm) • Tobacco filler mass (mg) • Cigar wrapper porosity (CU) • Cigar tip length (mm) (if applicable) • Cigar tip inner diameter (mm) (if applicable) • Cigar tip width (mm) (if applicable)

Table 10 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Leaf-Wrapped Cigars

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar mass (mg) • Cigar length (mm) • Cigar minimum diameter (mm) • Cigar maximum diameter (mm) • Tobacco moisture (%)	• Cigar mass (mg) • Cigar length (mm) • Cigar minimum diameter (mm) • Cigar maximum diameter (mm) • Tobacco moisture (%)

Table 11 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Cigar Tobacco

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (mm) • Tobacco moisture (%)	• Tobacco cut size (mm) • Tobacco moisture (%)

Table 12 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Cigar Wrappers

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar wrapper length (mm) • Cigar wrapper minimum width (mm) • Cigar wrapper maximum width (mm)	• Cigar wrapper length (mm) • Cigar wrapper minimum width (mm) • Cigar wrapper maximum width (mm)

Table 13 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Waterpipes

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Number of hoses • Bowl volume (ml)	• Bowl volume (ml)

Table 14 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Waterpipe Tobacco

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (mm) • Tobacco moisture (%)	• Tobacco cut size (mm) • Tobacco moisture (%)

Table 15 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Waterpipe Heating Sources

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Heating source type • Charcoal temperature (°C) (if applicable) • Coil temperature range (°C) (if applicable) • Power delivery unit (PDU) temperature cut-off (°C) (if applicable)	• Charcoal temperature (°C) (if applicable) • Coil temperature range (°C) (if applicable) • PDU temperature cut-off (°C) (if applicable)

Table 16 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Waterpipe Foil

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Foil length (mm) • Foil width (mm)	• Foil length (mm) • Foil width (mm)

Table 17 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Pipes

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Bore minimum diameter (mm) • Bore maximum diameter (mm) • Bit length (mm) • Bit diameter (mm) • Stem length (mm) • Stem diameter (mm)	• Bore minimum diameter (mm) • Bore maximum diameter (mm) • Bit length (mm) • Bit diameter (mm) • Stem length (mm) • Stem diameter (mm)

Table 18 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for Pipe Tobacco

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (mm) • Tobacco moisture (%)	• Tobacco cut size (mm) • Tobacco moisture (%)

Table 19 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for ENDS

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Airflow rate (cc/min) • Coil resistance (ohms) • Overall atomizer resistance (ohms) • Wick ignition temperature (°C) • Battery mAh rating (mAh) • PDU wattage operating range (W) • Coil temperature cut-off (°C) • Coil temperature range (°C) • ***Product software or technology (e.g., Bluetooth)***	• Airflow rate (cc/min) • Coil resistance (ohms) • Overall atomizer resistance (ohms) • Wick ignition temperature (°C) • Battery mAh rating (mAh) • PDU wattage operating range (W) • Coil temperature cut-off (°C) • Coil temperature range (°C) • ***Product software or technology (e.g., Bluetooth)***

Table 20 to § 1114.7(i)(2)(ii)--Required Design Parameter Information for E-liquids

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• E-liquid volume (ml)	• E-liquid volume (ml)

(iii) *Function*. How the product is intended to function.

(iv) Product *pH and nicotine formulation*. The pH of the product and the formulation of nicotine in the product, if applicable, including the form (e.g., unprotonated nicotine, nicotine salts) and quantity.

(v) *Fermentation process*. For those products that contain fermented tobacco, information on the fermentation process, including the following:

(A) Composition of the inoculum (starter culture) with genus and species name(s) and concentration(s) (if applicable);

(B) Any step(s) taken to reduce endogenous microbes (e.g., cleaning of product contact surfaces);

(C) Specifications and test data for pH, temperature, moisture content, and water activity;

(D) Frequency of aeration or turning (if applicable);

(E) Duration of fermentation;

(F) Added ingredients; and

(G) Method used to stabilize or stop (if applicable), fermentation, including data to demonstrate that the process is effective at reducing microbial content of the product and to suppress microbial activity of residual microorganisms to preclude further in-package fermentation.

(vi) *Storage and stability information*. The application must contain product storage and stability information that establishes the microbial and chemical stability of the product throughout the shelf life, including:

(A) A description of the shelf life and how it is indicated on the tobacco product, if applicable; ~~and~~

(B) Testing on the tobacco product in the same container closure system that will be used if granted a marketing order that was performed at the beginning (zero time), middle, and end of the expected storage time for the chemical and microbial endpoints for the following items: microbial content data, including total aerobic microbial count and total yeast and mold count along with identification of detected microbiological organisms by genus and species names, if applicable; pH; moisture content; water activity; tobacco-specific nitrosamines (TSNAs) (reported as separate amounts for the total TSNAs, NNN (N′-nitrosonor-nicotine), NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)); nitrate and nitrite levels; preservatives and microbial metabolic inhibitors (if any); and method of heat treatment, pasteurization, or other method used to reduce microbial loads***;***

(C) Detailed plans for monitoring products that have been in storage too long and for removing these products from the market in a timely manner; and

(D) If granted a marketing order, applicants must provide regular postmarket reports that describe how much product has been removed, the reason for the removal, and details

about how the product was disposed.

(vii) *Product and packaging design risks and misuse hazards*. A review and assessment of reasonably foreseeable risks associated with the design of the tobacco product and its package that may occur during normal use of the tobacco product or during any foreseeable misuse of the product, including user error, which may cause illness, injury, or death not normally associated with the use of the tobacco product. The review and assessment must identify the measures taken to reduce or eliminate each risk associated with the design of the tobacco product and package.

(3) *Principles of operation*. The applicant must provide a full statement of the principle or principles of operation of the tobacco product, including full narrative descriptions of:

(i) The way in which a typical consumer will use the new tobacco product, including a description of how a consumer operates the product and, where applicable, can change the product design and add or subtract ingredients;

(ii) The length of time it takes for a user to consume a single unit of the product***, and, for electronic nicotine delivery systems, details about the software or other controls in the device to limit the intensity of use, including but not limited to minimum inter-puff interval and maximum number of puffs per hour that the device will deliver***; and

(iii) Whether the product incorporates a heating source, and if so, a description of the heating source.

(4) *Product testing and analysis information*. Each analysis required in this paragraph must be performed on test samples that reflect the finished tobacco product composition and design, and must be conducted using a sufficient sample size and number of replicates to substantiate the results of the type of testing conducted. Additionally, the applicant must provide the following information:

(i) The name and location of the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally

recognized external accreditation organization;

(ii) The length of time between dates of manufacture and date(s) of testing;

(iii) The storage conditions of the tobacco product before it was tested;

(iv) The number of samples and measurement replicates for each sample;

(v) A description of method procedure, method validation information and rationale for selecting each test method, including relevant voluntary testing standards, test protocols, quantitative acceptance criteria, line data, and a summary of the results;

(vi) Reports of product formulation testing that include test protocols, quantitative acceptance criteria, line data, and a summary of the results, for each applicable parameter; and

(vii) Complete descriptions of any smoking or aerosol-generating regimens used for analytical testing that are not standardized or widely accepted by the scientific community, if applicable.

(j) *Manufacturing*. The application must contain a full description of the methods used in, and the facilities and controls used for, the design (including design validation and design verification, to assess whether the tobacco product, as manufactured, performs in accordance with design specifications), manufacture, packing, and storage of the tobacco product in sufficient detail to demonstrate whether the product meets manufacturing specifications, can be manufactured in a manner consistent with the information submitted in the application, and conforms to the requirements of any regulations issued under section 906(e) of the Federal Food, Drug, and Cosmetic Act, including:

(1) A list of all manufacturing, packaging, storage, and control facilities for the product, including the facilities name, address, and FEI number, if applicable, and a contact name and telephone number for a representative from each facility;

(2) A narrative description, accompanied by a list and summary, of all standard operating

procedures (SOPs) and examples of relevant forms and records for the following categories of information for all manufacturing, design controls, packing, and storage for the tobacco product:

(i) Manufacturing and production process activities at each establishment, including a description of each establishment, all production steps, and process controls, process specifications with relevant acceptance criteria, and monitoring and acceptance activities;

(ii) Managerial oversight and employee training related to the manufacture, processing, packing, and installation of the tobacco product, as applicable;

(iii) Monitoring procedures and manufacturing controls for product design, product characteristics, and changes in products, specifications, methods, processes, or procedures, including a hazard analysis that details the correlation of the product design attributes with public health risk, as well as any mitigation strategies implemented;

(iv) Activities related to identifying and monitoring suppliers and the products supplied (including, for example, purchase controls and product acceptance activities);

(v) Handling of complaints, nonconforming products and processes, and corrective and preventative actions;

(vi) Testing procedures carried out before the product is released to market, including:

(A) A list and summary of any standards used for all testing methods;

(B) Validation and verification activities for all test methods used to ensure that the tobacco product meets specifications;

(C) Documentation of accreditation information for all testing laboratories;

(D) Complete description of smoking or aerosol-generating regimes used for analytical testing, if any; and

(E) Tobacco product specifications (including any physical, chemical, and biological specifications) and acceptance criteria for those specifications;

(F) Reports of release testing performed on finished products to demonstrate conformity with established specifications, including test protocols, line data, and a summary of the results for each applicable testing.

(k) *Health risk investigations*--(1) *Study types*. The application must contain full reports of all information***, including evidence about actual use in the real world, including actual use patterns and health effects of similar products or products that were on the market prior to submitting the application, and*** including the substantive information required by § 1114.27(b)(1)(ii) for application filing, both favorable and unfavorable, published or known to, or which should reasonably be known to, the applicant concerning investigations, including nonclinical and human subject studies, which have been made to show:

(i) *Health risks of the product*. The potential health risks of the tobacco product to users and nonusers, including potential exposures, and whether the product may present different risks than ***all*** other tobacco products, including:

(A) The health effects of the constituents, including HPHCs, at the quantitative levels delivered to both users and nonusers under the range of conditions under which the product might be ***or is actually*** used;

(B) The toxicological profile of the new tobacco product related to the route of administration, including the ***cardiovascular effects (including effect on blood), respiratory effects,*** genotoxicity, carcinogenicity, reproductive ***toxicity (including the intergenerational health effects caused by epigenetic changes)***, immunotoxicity, acute toxicity, and repeat dose (chronic) toxicity of the new tobacco product, including those relative to ***all*** other tobacco products. ***The applicant must provide comparable toxicological information for dual users, and specify the quantity of toxicants to which the dual- and/or poly-user will be exposed and the biological and clinical effects of dual- and/or poly-exposure as compared with using the***

product alone. The toxicological profile also includes information on the toxicity of the ingredients, additives, and HPHCs, relative to the route of administration and the range of potential levels of exposure resulting from the use of, or exposure to, the new tobacco product, including studies which discuss the toxicological effects of any leachables and extractables that can appear from the container closure system and the ingredient mixture, such as additive or synergistic effects;

(C) The pharmacological profile of the new tobacco product, including the pharmacokinetics, pharamacodynamics, metabolism, and elimination profile, of any of the ingredients, additives, and HPHCs for the range of potential levels of exposure resulting from the use of, or exposure to, the new tobacco product relative to all other tobacco products. The applicant must specify whether the studies were conducted in vitro, in vivo, ex vivo, or in silico; and

(D) The health risks of the tobacco product compared to ***all*** other tobacco products on the market, never using tobacco products, quitting tobacco product use, and using the tobacco product in conjunction with other tobacco products. ***The applicant must provide meaningful estimates of levels of dual- and poly-use based on their own and independent research for the proposed product if available, and/or comparable products.***

(ii) *Impacts on tobacco use behavior of tobacco product users*. How the product and its label, labeling, and advertising will affect the tobacco use behavior of tobacco product users, including:

(A) The abuse liability of the tobacco product. ***The applicant must provide real world, actual use data relevant to the product's abuse liability, including misuse, that is known or available to the applicant;***

(B) How users actually use the product, including use topography, product use frequency, use trends over time, and how such use affects the health risks of the product to individual users;

(C) The likelihood that users will use the product in conjunction with ***one or more of all*** other tobacco products ***on the market***;

(D) The likelihood that current tobacco product users will start using the product;

(E) The likelihood that current tobacco users who adopt the product will switch to or switch back to other tobacco products that may present increased risks to individual health; and

(F) The likelihood that current tobacco users who may have otherwise quit using tobacco products will instead start or continue to use the product.

(iii) *Impacts on tobacco use initiation by nonusers, including youth and young adults*. The impact of the tobacco product, its label, labeling, and advertising on tobacco use initiation by nonusers, including:

(A) The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product;

(B) The likelihood that nonusers of tobacco products who adopt the tobacco product will switch to other tobacco products that may present higher levels of individual health risk; and

(C) The likelihood that former users of tobacco products will re-initiate use with the tobacco product.

(iv) *Perceptions and use intentions*. The impact of the product and its label, labeling, and advertising on individuals:

(A) Perception of the product;

(B) Use intentions; and

(C) Ability to understand the labeling and instructions for use and use the product in accordance with those instructions.

(v) *Human factors*. The impact of human factors on product risk, including discussion of use conditions, use environments, use related hazards, estimated use error risk, potential

unintended uses, risk controls to ensure that harms and unintended consequences are minimized, and adverse experiences related to such uses.

(2) *Literature search*. The applicant must conduct a ***full*** literature search for each type of information described in paragraph (k)(1) of this section, and the application must contain a description of the literature search performed, including the databases searched and the date searched, search terms, reasons for inclusion or exclusion of documents, and the strategy for study quality assessment. The application must also contain a bibliography of all published studies and articles referenced in the application. ***The applicant must provide the sources of support (i.e., industry or independent funding) of all studies submitted in support of the application.*** If a literature search was performed and resulted in no information found, the application must contain a statement to that effect.

(3) *Study reports*. The full report of each study included in the application must describe the specific product studied and include the following items, where applicable and to the extent reasonably available. For applicable items not contained in the full report of an investigation, the applicant must contain a description of the actions taken to obtain the information and why the document is not reasonably available.

(i) Full copies of any published articles and other reference materials;

(ii) Documentation of all actions taken to ensure the reliability of the study. For nonclinical laboratory studies, the application must contain, for each study, documentation of all actions taken to ensure the reliability of the study, e.g., documentation of whether the study was conducted in accordance with good laboratory practices, such as those specified in part 58 of this chapter. For studies involving human subjects, to the extent reasonably available or obtainable, the application must contain a certification that clinical investigators do not have, or documentation fully disclosing, any financial conflicts of interest, such as the financial arrangements specified in the Financial Disclosure by Clinical Investigators regulation in part 54

of this chapter;

(iii) Copies of all versions of protocols and amendments that were used in the study;

(iv) Copies of all versions of investigator instructions, if any were produced in addition to the protocol;

(v) The statistical analysis plan, including a detailed description of the statistical analyses used (including all variables, confounders, and subgroup analyses), the scientific rationale for the choice of sample sizes, and any amendments to the plan. ***The applicant must also report the minimum detectable effect with 95% power for the sample sizes used in the applicant's studies***;

(vi) Line data, including data definition files that include the names of the variables, codes, and formats in each dataset, and copies of programs and any necessary macro-programs used to create derived datasets, and the results included in the study reports;

(vii) A list of sites and clinical investigators that conducted the study, including contact information and physical address(es);

(viii) The location of all source data. If the site where the study was conducted has not maintained all of the source data, indicate where the data are located;

(ix) The format of the records and data (e.g., electronic or hard copy);

(x) A list of all sites that had early termination and the reason for early termination, along with any audit certificates and inspection results, if applicable;

(xi) A list of contractors who participated in the study, the role of each contractor, and the initiation and termination dates of the participation of each contractor;

(xii) A signed full report of all findings;

(xiii) For human subject studies:

(A) All versions of study materials (e.g., consent forms, questionnaires, stimuli) used;

(B) All versions of case report forms used; and

(C) Individual case report forms related to participant deaths, other serious and unexpected adverse experiences, withdrawals, and participant discontinuation where the study participant was exposed to the tobacco product that is the subject of the PMTA or similar products; and

(xiv) For tobacco product perception and use intention studies that use advertising as stimuli, a statement describing whether the advertising used is representative of advertising that the applicant intends to use in marketing the product. If the advertising is not representative of the advertising an applicant intends to use in marketing the product, the applicant must describe whether the study results are still relevant to the likely impact of the advertising on tobacco product perceptions and use intentions.

(l) *The effect on the population as a whole*. The application must contain an analysis and discussion of how the data and information contained in the application establish that permitting the tobacco product to be marketed would be appropriate for the protection of public health determined with respect to the population as a whole, including users and nonusers of the tobacco product. ***The applicant must affirm that no partners, sponsors, influencers, bloggers, or brand ambassadors have been or will be used to create labeling for, market, advertise, or promote the product.*** The analysis and discussion must integrate all of the information regarding the product and its likely effects on health, and tobacco use behavior, including tobacco use cessation and initiation, to provide an overall assessment of the likely effect that the marketing of the tobacco product may have on overall tobacco-related morbidity and mortality.

(m) *Certification statement*. The application must contain the following certification, with the appropriate information inserted (as indicated by parenthetical italicized text), signed by an authorized representative of the applicant:

"I (*name of responsible official*) on behalf of the applicant, (*applicant name*), hereby certify that the applicant will maintain all records to substantiate the accuracy of this application for the period of time required in

21 CFR 1114.45 and ensure that such records remain readily available to FDA upon request. I certify that this information and the accompanying submission are true and correct, that no material fact has been omitted, and that I am authorized to submit this on the applicant's behalf. I understand that under section 1001 of title 18 of the United States Code anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

§ 1114.9 Amendments.

(a) *General*. FDA may request, or an applicant may submit on its own initiative, an amendment to a PMTA containing information that is necessary for FDA complete the review of a pending PMTA. An amendment must include the appropriate form and specify the STN assigned to the original submission and, if submitted other than at FDA's request, the reason for submitting the amendment. An amendment must also include the certification statement set forth in § 1114.7(m), with the appropriate information inserted, and signed by an authorized representative of the applicant.

(b) *Review of an amendment*. Submission of an amendment may affect the timing of review of an amended submission as follows:

(1) If the amendment is a major amendment (e.g., an amendment that contains significant new data from a previously unreported study, detailed new analyses of previously submitted data), FDA may restart the 180-day review period after receipt of the amendment.

(2) If FDA requests a minor amendment (i.e., an amendment that is not a major amendment) and receives a written response submitting the requested amendment, FDA may pause the review period for the number of days elapsed between the date of the request and the date that FDA receives the written response.

(c) *Failure to respond to amendment request*. If FDA requests an amendment and the applicant does not respond within 180 days of FDA's request, FDA may consider the applicant

to have submitted a request to voluntarily withdraw the pending PMTA under § 1114.11 and issue an acknowledgment letter notifying the applicant of the withdrawal.

(d) *No amendment to closed or withdrawn application*. An applicant may not amend an application after FDA has closed the application through an action under § 1114.29 or it has been withdrawn under § 1114.11.

§ 1114.11 Withdrawal by applicant.

(a) An applicant may at any time make a written request using the appropriate form to withdraw a PMTA that FDA has not acted on as described in § 1114.29. The withdrawal request must state:

(1) Whether the withdrawal is due to a health concern related to the tobacco product and, if so, a description of those concerns, including the extent, duration, and frequency of the health effects, and what gave rise to the concerns, such as reports of adverse experiences;

(2) The application STN; and

(3) The name(s) of the new tobacco product that is the subject of the application.

(b) An application will be considered withdrawn when FDA issues an acknowledgement letter stating that the application has been withdrawn.

(c) The application is an Agency record, even if withdrawn. FDA will retain the withdrawn application under Federal Agency records schedules. The availability of the withdrawn application will be subject to FDA's public information regulation in § 20.45 of this chapter.

§ 1114.13 Change in ownership of an application.

An applicant may transfer of ownership of a PMTA. At or before the time of transfer, the new owner and the former owner must submit information to FDA using the appropriate form as follows:

(a) The new and former owner must sign and submit a notice to FDA stating that all of the former applicant's rights and responsibilities relating to the PMTA have been transferred to the new owner. This notice must identify the name and address of the new owner and the PMTA transferred by tobacco product name(s) and STN.

(b) The new owner must sign and submit a notice to FDA containing the following:

(1) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application and marketing order, if applicable;

(2) The date that the change in ownership is effective;

(3) Either a statement that the new owner has a complete copy of the application, including all amendments, the marketing order (if applicable), and any records that are required to be kept under § 1114.45, or a request for a copy of the application, including all amendments, and the modified risk order (if applicable) from FDA's files in accordance with part 20 of this chapter. In accordance with the Freedom of Information Act, FDA will provide a copy of the application to the new owner under the fee schedule in FDA's public information regulations in § 20.45 of this chapter; and

(4) A certification that no modifications have been made to the tobacco product since the application, including amendments (if any), was submitted to FDA.

§ 1114.15 Supplemental applications.

(a) *Supplemental PMTA submission*. Applicants that have received a marketing order for a tobacco product may, as an alternative format of submitting an application that meets the content requirements of § 1114.7, submit a supplemental PMTA to seek marketing authorization for modifications to such product, which result in a new tobacco product under 910(a)(1) of the Federal Food, Drug, and Cosmetic Act. Supplemental PMTAs must include new information

concerning modifications that create the new tobacco product but allow the applicant to satisfy the remaining application requirements by cross-referencing applicable content from the previously submitted PMTA for the original tobacco product. ***Supplemental PMTAs must include information on any changes to the software or device that could result in two-way communication with the device and/or reprogramming of the nicotine delivery pattern (whether this reprogramming of the nicotine delivery pattern is automatic or as the result of two-way communication with the device).*** Applicants may submit supplemental PMTAs only for modifications that require the submission of limited new information. An applicant may not submit a supplemental PMTA where:

(1) Modifications to the product that result in the new tobacco product require the submission of new information or revisions to the PMTA for the original product to the extent that reviewing a supplemental application for the new tobacco product would be confusing, cumbersome, or otherwise inefficient and submitting a standard PMTA under § 1114.7 would better facilitate review.

(2) The marketing order for the original tobacco product has been withdrawn; or

(3) The marketing order for the original tobacco product has been temporarily suspended or is subject to temporary suspension or withdrawal proceedings by FDA, except where authorized in writing by FDA following a presubmission meeting.

(b) *Required format.* The supplemental PMTA must comply with format requirements of § 1114.7(b), except that an applicant must include content in a supplemental PMTA by cross-referencing a PMTA, or, where applicable, a supplemental PMTA, for an original tobacco product that is owned by that applicant and may include content by cross-referencing a tobacco product master file and postmarket reports for the original tobacco product. FDA will not consider content included by cross-reference to other sources of information outside of the

submission.

(c) *Required content*. The supplemental PMTA must provide sufficient information for FDA to determine whether any of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply to the application.

(1) The application must contain the full text of all the information described in the following sections:

(i) General information that identifies the submission as a supplemental PMTA (as described in § 1114.7(c));

(ii) New product information (as described in paragraph (d) of this section);

(iii) Statement of compliance with part 25 of this chapter (as described in § 1114.7(g));

(iv) Labeling (as described in § 1114.7(f)) if the labeling is not identical to the labeling submitted in the PMTA or postmarket reports for the original product;

(v) Postmarket information (as described in paragraph (e) of this section); and

(vi) Certification statement (as described in paragraph (f) of this section);

(2) The application must include the following sections by cross-reference to the PMTA for the original tobacco product and contain any additional information that is necessary to supplement or update the cross-referenced information:

(i) Descriptive information (as described in § 1114.7(d));

(ii) Product samples (as described in § 1114.7(e));

(iii) Labeling (as described in § 1114.7(f)) if the labeling is identical to the labeling that was submitted in the PMTA or postmarket reports for the original tobacco product;

(iv) Summary of all research findings (as described in § 1114.7(h));

(v) Product formulation (as described in § 1114.7(i));

(vi) Manufacturing (as described in § 1114.7(j)); and

(vii) Health risk investigations (as described in § 1114.7(k)).

(d) *New product information*. The application must contain a section that includes:

(1) Full descriptions of each modification to the product and comparisons to the original product version described in the previously authorized PMTA;

(2) A statement as to whether the new tobacco product, if it receives a marketing order, will replace the original tobacco product, will be a line extension of the original tobacco product, or will be introduced as an additional product by the same manufacturer;

(3) All data and information relating to each modification to the product that would be required in an application under § 1114.7; and

(4) A concluding summary of how the new tobacco product meets the requirements to receive a marketing order, including how the data and information contained in both the supplemental PMTA and cross-referenced from the previously authorized PMTA constitute valid scientific evidence and establishes that the PMTA meets the requirements of section 910(c) of the Federal Food, Drug, and Cosmetic Act to receive a marketing order, including that permitting the new tobacco product to be marketed would be appropriate for the protection of the public health determined with respect to the risks and benefits on the population as a whole, including users and nonusers of the tobacco product.

(e) *Postmarket reports*. (1) If an applicant has submitted postmarket reports for the original tobacco product, the applicant must include all such reports in the application by cross-reference.

(2) If an applicant is required to, but has not yet submitted a postmarket report, the applicant must submit a report as part of its application of all information required under §

1114.41 covering the period of time from when it received a marketing order to when it submits the supplemental PMTA.

(f) *Certification statement*. The application must contain the following certification, with the appropriate information inserted as indicated by parenthetical italicized text, signed by an authorized representative of the applicant:

"I, (*name of responsible official*), on behalf of (*name of applicant*), certify that (*new tobacco product name*) has a different (*describe each modification to the product*) than (*name of original tobacco product*) described in (*STN of the PMTA for the original product*) but is otherwise identical to (*name(s) of original tobacco product*). I certify that (*name of applicant*) understands this means there is no other modification to the materials, ingredients, design, composition, heating source, or any other feature of the original tobacco product. I also certify that (*name of applicant*) will maintain all records that substantiate the accuracy of this application and ensure that such records remain readily available to FDA upon request for the period of time required in 21 CFR 1114.45. I certify that this information and the accompanying submission are true and correct, and that I am authorized to submit this on the applicant's behalf. I understand that under section 1001 of title 18 of the United States Code, anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

§ 1114.17 Resubmissions.

(a) *General*. An applicant may, as an alternative format of submitting an application that meets the content requirements of § 1114.7 or § 1114.15 (if applicable), submit a resubmission to address deficiencies set forth in a no marketing order. The resubmission must contain new information necessary to address application deficiencies and cross-reference applicable content from the PMTA that received the no marketing order. An applicant may utilize the resubmission format for the same tobacco product for which FDA issued a no marketing order or a new tobacco product that results from modifications to the product necessary to address the

deficiencies described in a no marketing order. An applicant may not submit a resubmission when:

(1) It incorporates new information or revisions to the PMTA for the original product to the extent that reviewing a resubmission for the new tobacco product would be confusing, cumbersome, or otherwise inefficient and submitting a standard PMTA under § 1114.7 would better facilitate review; or

(2) The no marketing order states that the applicant may not submit a resubmission.

(b) *Required format.* The resubmission must comply with format requirements of § 1114.7(b), except that an applicant must include content in the resubmission by cross-referencing the PMTA, or, where applicable, supplemental PMTA, that received the no marketing order. FDA will not consider content included by cross-reference to other sources of information outside of the submission.

(c) *Required content*. The resubmission must provide sufficient information for FDA to determine whether any of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply to the application.

(1) The application must include the full text of the information described in the following paragraphs:

(i) General information that identifies the submission as a resubmission (as described in paragraph § 1114.7(c));

(ii) Response to deficiencies (as described in paragraph (d) of this section); and

(iii) Certification statement (as described in paragraph (e) of this section).

(2) The application must include the following sections from the PMTA that received a no marketing order by cross-reference and contain all additional information that is necessary to supplement or update the cross-referenced information:

(i) Descriptive information (as described in § 1114.7(d));

(ii) Product samples (as described in § 1114.7(e));

(iii) Labeling (as described in § 1114.7(f));

(iv) Statement of compliance with part 25 of this chapter (as described in § 1114.7(g));

(v) Summary of all research findings (as described in § 1114.7(h));

(vi) Product formulation (as described in § 1114.7(i));

(vii) Manufacturing (as described in § 1114.7(j)); and

(viii) Health risk investigations (as described in § 1114.7(k)).

(d) *Response to deficiencies*. (1) The application must include a section that lists and provides a separate response to each deficiency described by FDA in the original no marketing order, including all data and information necessary to complete each response, and also addresses any applicant-identified deficiencies.

(2) Where an applicant modifies the product in a way that would result in a new tobacco product under section 910(a)(1) of the Federal Food, Drug, and Cosmetic Act in order to address the deficiencies, the application must also include:

(i) A full description of each modification to the product and comparisons of that change to the original version described in the previously submitted PMTA; and

(ii) All data and information relating to each modification to the product that would be required in an application under § 1114.7.

(e) *Certification statement*. The application must contain the following certification that corresponds to the application, with the appropriate information inserted as indicated by parenthetical italicized text, signed by an authorized representative of the applicant.

(1) *Same tobacco product certification*. An application for the same tobacco product must contain the following certification:

"I, (*name of responsible official*), on behalf of (*name of applicant*), certify that this submission for (*new tobacco product name(s)*) responds to all deficiencies outlined in the no marketing order issued in response to (*STN of the previously submitted PMTA*) and the new tobacco product described herein is identical to the product described in the previously submitted PMTA. I certify that (*name of applicant*) understands this means there is no modification to the materials, ingredients, design, composition, heating source, or any other feature. I also certify that (*name of applicant*) will maintain all records that substantiate the accuracy of this statement, and ensure that such records remain readily available to FDA upon request for the period of time required in 21 CFR 1114.45. I certify that this information and the accompanying submission are true and correct, and that I am authorized to submit this on the company's behalf. I understand that under section 1001 of title 18 of the United States Code, anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

(2) *Different tobacco product certification*. An application for a different tobacco product than the original tobacco product that results from changes necessary to address the deficiencies must contain the following certification:

"I, (*name of responsible official*), on behalf of (*name of applicant*), certify that this submission for (*new tobacco product name(s)*) responds to all deficiencies outlined in the no marketing order issued in response to (*STN of the previously submitted PMTA*) and the new tobacco product described herein has a different (*describe each modification to the product*) than (*name(s) of original tobacco product*) described in (*STN of the previously submitted PMTA*) but is otherwise identical to (*name(s) of original tobacco product*) described in (*STN of the previously submitted PMTA*). I certify that (*name of applicant*) understands this means there is no modification to the materials, ingredients, design features, heating source, or any other feature of the original tobacco product,

except for the (*describe each modification to the tobacco product*). I also certify that (*name of applicant*) will maintain all records that substantiate the accuracy of this statement, and ensure that such records remain readily available to FDA upon request for the period of time required in 21 CFR 1114.45. I certify that this information and the accompanying submission are true and correct, and that I am authorized to submit this on the company's behalf. I understand that under section 1001 of title 18 of the United States Code, anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

Subpart C--FDA Review

§ 1114.25 Communication between FDA and applicants.

During the course of reviewing an application, FDA may communicate with an applicant about relevant matters, including scientific, medical, and procedural issues that arise during the review process and inspections. These communications may take the form of telephone conversations, letters, electronic communications, or meetings, and will be documented in the administrative file in accordance with § 10.65 of this chapter.

§ 1114.27 Review procedure.

(a) *Acceptance review*. (1) After an applicant submits a PMTA, FDA will perform an initial review of the PMTA to determine whether it may be accepted for further review. FDA may refuse to accept an application that:

(i) Does not comply with the applicable format requirements in § 1114.7(b), § 1114.15, or § 1114.17 (as applicable);

(ii) Is not administratively complete because it does not appear to contain the information required by § 1114.7 (excluding product samples), § 1114.15, or § 1114.17, as applicable;

(iii) Does not pertain to a tobacco product subject to chapter IX of the Federal Food, Drug, and Cosmetic Act (as required by § 1105.10 of this chapter); or

(iv) FDA can otherwise refuse to accept under § 1105.10.

(2) If FDA accepts an application for further review, FDA will issue an acknowledgement letter to the applicant that specifies the PMTA STN. If FDA determines that it will require product samples as part of the PMTA, it will send instructions on how and where to submit product samples, as described in § 1114.7(e) of this chapter.

(3) If FDA refuses to accept an application, FDA will issue a letter to the applicant identifying the deficiencies, where practicable, that prevented FDA from accepting the application.

(b) *Filing review*. (1) After accepting a PMTA, FDA will make a threshold determination of whether the application contains sufficient information to permit a substantive review. FDA may refuse to file a PMTA if any of the following applies:

(i) The PMTA does not include sufficient information required by section 910(b)(1)(A) through (b)(1)(F) of the Federal Food, Drug, and Cosmetic Act and by § 1114.7, § 1114.15, or § 1114.17, as applicable, to permit a substantive review of the application;

(ii) The application does not contain any information, including information from published literature or bridged from an investigation of another tobacco product, regarding:

(A) The health risks of the new tobacco product (as described in § 1114.7(k)(1)(i)(A) through (C));

~~(B)~~ The health risks of the new tobacco product compared to the health risks generally presented by ***all other products currently on the market***~~both products in the same product category and products in at least one different category that are used by the consumers an applicant expects will use its new tobacco product (as set forth in a portion of § 1114.7(k)(1)(i)(D)).~~

(C) The abuse liability of the new tobacco product (as set forth in § 1114.7(k)(1)(ii)(A));

(D) How consumers would be expected to actually use the product, including use frequency, use trends over time, and how such use affects the health risks of the product to individual users (as set forth in § 1114.7(k)(1)(ii)(B));

(E) The impact that marketing the new tobacco product would have on the likelihood that current tobacco product users would start using the new tobacco product, use the product in conjunction with other tobacco products, and, after using the product, switch to or switch back to other tobacco products that may present increased risks to individual health (as set forth in § 1114.7(k)(1)(ii)(C) through (F));

(F) The impact that the marketing of the new tobacco product would have on tobacco product use behavior of current nonusers of tobacco products (as described in § 1114.7(k)(1)(iii)); or

(G) The impact of the product and its label, labeling, and advertising on individuals' perception of the product and their use intentions (as described in § 1114.7(k)(1)(iv));

(iii) The PMTA contains a false statement of material fact;

(iv) The PMTA is a supplemental PMTA that does not comply with § 1114.15; or

(v) The PMTA is a resubmission that does not comply with § 1114.17.

(2) If FDA refuses to file an application, FDA will issue a letter to the applicant identifying the deficiencies, where practicable, that prevented FDA from filing the application.

(3) If FDA files an application, FDA will issue a filing letter to the applicant.

(c) *Application review*. (1) Except as described in this paragraph and § 1114.9(b), within 180 days of receipt of an application described in section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act, FDA will complete its review of the PMTA and act on the application.

(2) FDA will begin substantive review of the application after it is filed under paragraph (b) of this section. FDA may communicate with the applicant as set forth under § 1114.25 to seek additional or clarifying information.

(3) ***FDA shall make all PMTAs publicly available (except for matters in the application which are trade secrets or otherwise confidential, commercial information) and shall consider comments submitted by interested persons. FDA shall refer PMTAs from major tobacco companies (larger than XX) to TPSAC for submission of a report and recommendation respecting the application, together with all underlying data and the reasons or basis for the recommendation.*** FDA may refer ~~the~~***any other*** PMTA or portions of the PMTA, upon its own initiative or applicant request, to TPSAC for reference and for the submission of a report and recommendation respecting the application, together with all underlying data and the reasons or basis for the recommendation.

(4) FDA may conduct inspections of the applicant's manufacturing sites, and sites and entities involved with clinical and nonclinical research (including third parties and contract research organizations) to support FDA's review of the PMTA. Where an applicant prevents FDA from scheduling and conducting inspections that are necessary for FDA to complete its review of the PMTA in a timely manner, FDA may pause the 180-day review period for the number of days necessary to complete the inspection.

(5) FDA may defer review of a PMTA for a new product that, if introduced or delivered for introduction into interstate commerce, would be adulterated or misbranded due to the manufacturer or importer's failure to comply with user fee payment and reporting requirements under part 1150.

§ 1114.29 FDA action on an application.

After receipt of an application, FDA will:

(a) Refuse to accept the application as described in § 1114.27(a);

(b) Issue a letter administratively closing the application;

(c) Issue a letter canceling the application if FDA finds that it mistakenly accepted the application or that the application was submitted in error;

(d) Refuse to file the application as described in § 1114.27(b);

(e) Issue a marketing order as described in § 1114.31; or

(f) Issue a no marketing order as described in § 1114.33.

§ 1114.31 Issuance of a marketing order.

(a) FDA will issue a marketing order if it finds that none of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply. A marketing order becomes effective on the date it is issued.

(b) FDA may include, as part of the marketing order:

(1) Restrictions on the sale and distribution of the product, including restrictions on the access to, and the advertising and promotion of, the tobacco product, to the extent that it would be authorized to impose such restrictions under a regulation issued under section 906(d) of the Federal Food, Drug, and Cosmetic Act;

(2) Any restrictions on the sales, distribution, advertising, and promotion of the new tobacco product that the applicant proposed to be included as part of a marketing order under section 910(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act to help FDA make the finding that permitting the product to be marketed would be appropriate for the protection of the public health; and

(3) Requirements to establish and maintain records, and submit postmarket reports under section 910(f) of the Federal Food, Drug and Cosmetic Act in addition to those described in § 1114.41, including but not limited to information such as labeling, advertising, marketing,

promotional materials, or marketing plans not previously submitted to FDA ***at least 30 days before initial publication, dissemination to consumers, or use and engaging or communicating with consumers of such materials.***

(c) During the initial five-year marketing period, all advertising and marketing materials must be preauthorized by FDA.

§ 1114.33 Issuance of a no marketing order.

(a) *Issuance*. FDA will issue a no marketing order if:

(1) FDA finds that any of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply. ***In particular, when considering whether there is a lack of a showing that permitting the product to be marketed is appropriate for the protection of the public health, FDA must consider dual- and/or poly-use of the product and deterrence of complete quitting of all tobacco products;***

(2) The application does not include specific assurances supported by evidence that there will be no communication between the device and any external source, and that nothing in the product's software or technology can or will be programmed to increase consumption;

(3) FDA is unable to determine the impact that the labeling, advertising, marketing, and promotion of the new tobacco product may have on consumer perceptions (including the perceptions of youth and young adults) and use intentions;

(4) The applicant uses partners, sponsors, influencers, bloggers, or brand ambassadors to create labeling for, market, advertise, or promote their product;

(5) FDA finds, after considering outside sources of information during PMTA review, that the new tobacco product is not appropriate for the protection of the public health;

(6) The applicant does not permit an authorized FDA employee, at a reasonable time and in a reasonable manner, an opportunity to:

(i) Inspect the facilities and controls described in the application; or

(ii) Have access to, copy, and verify all records pertinent to the application,

which results in FDA finding that one or more of the grounds for denial specified in section 910(c)(2) of the Federal Food, Drug and Cosmetic Act apply.

(b) *Description of deficiencies*. The no marketing order will, where practicable, identify measures to remove the application from deniable form.

§ 1114.35 Withdrawal of a marketing order.

(a) *Grounds for withdrawal*. FDA ~~may~~ ***shall*** withdraw a marketing order for a new tobacco product issued under this part if FDA determines that:

(1) Any of the grounds for withdrawal under section 910(d)(1) of the Federal Food, Drug, and Cosmetic Act apply; or

(2) Any postmarket requirement imposed by the marketing order or by this part has not been met, which results in FDA finding that one or more of the grounds for withdrawal specified in section 910(d)(1) of the Federal Food, Drug and Cosmetic Act apply;

(3) The applicant used partners, sponsors, influencers, bloggers, or brand ambassadors to create labeling for, market, advertise or promote the tobacco product.

(b) *Advice and other information*. (1) FDA may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw a marketing order.

(2) FDA may use information other than that submitted by the applicant in deciding whether to withdraw a marketing order.

(c) *Informal hearing*. Prior to withdrawing a marketing order, FDA will offer the holder of the marketing order an opportunity for an informal hearing under part 16 of this chapter.

(d) *Order issuance*. If the applicant does not request a hearing or, if after the part 16 hearing is held, the Agency decides to proceed with the withdrawal, FDA will issue to the holder of the marketing order an order withdrawing the marketing order for the new tobacco product.

(e) *Public notice*. FDA will give the public notice of an order withdrawing a marketing order for a tobacco product and will announce the basis of the withdrawal.

§ 1114.37 Temporary suspension of a marketing order.

(a) FDA will temporarily suspend a marketing order if FDA determines that there is a reasonable probability that the continued distribution of such tobacco product would cause serious, adverse health consequences or death, that is greater than ordinarily caused by tobacco products on the market.

(b) Before temporarily suspending a marketing order of a tobacco product, FDA will offer the holder of the marketing order an opportunity for an informal hearing under part 16 of this chapter.

(c) If, after offering the holder of the marketing order an opportunity for a part 16 hearing, the Agency decides to proceed with the temporary suspension, FDA will issue an order temporarily suspending the marketing order for a tobacco product.

(d) After issuing an order temporarily suspending the marketing order, FDA will proceed expeditiously to initiate proceedings to withdraw the marketing order for the tobacco product.

Subpart D--Postmarket Requirements

§ 1114.39 Postmarket changes.

A marketing order authorizes the marketing of a new tobacco product in accordance with the terms of the order. Prior to the introduction or delivery for introduction into interstate commerce of a new tobacco product that results from modification(s) to the product, an applicant must submit a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and obtain a marketing order for the new tobacco product, unless the new tobacco product can be legally marketed through another premarket pathway.

§ 1114.41 Reporting requirements.

(a) *Required reports*. Except as specified in § 1114.43, each applicant that receives a marketing order must submit to FDA all information required by the terms of the marketing order and by this section as described below. Each postmarket report must be well-organized, legible, and written in English. Documents that have been translated from another language into English (e.g., original study documents written in a language other than English) must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation.

(1) *Periodic reports*. Each applicant must submit a periodic report to the Center for Tobacco Products (CTP) within 60 calendar days of the reporting dates specified in the applicant's marketing order for the life of the order and as may be required for the submission of a supplemental PMTA under § 1114.15. The report must include the following:

(i) A cover letter that contains the PMTA STN, tobacco product name(s) (including the original name described in the PMTA if different), company name, date of report, and reporting period;

(ii) A description of all changes made to the manufacturing, facilities, or controls during the reporting period, including:

(A) A comparison of each change to what was described in the PMTA;

(B) The rationale for making each change and, if any, a listing of any associated changes; and

(C) The basis for concluding that each change does not result in a new tobacco product that is outside the scope of the marketing order and will not result in a finding that the marketing order must be withdrawn or temporarily suspended under section 910(d) of the Federal Food, Drug, and Cosmetic Act;

(iii) An inventory of ongoing and completed studies about the tobacco product conducted by, or on behalf of, the applicant, that have not been previously reported;

(iv) Full reports of information published or known to, or which should be reasonably known to, the applicant concerning scientific investigations and literature about the tobacco product that have not been previously reported, as well as significant findings from publications not previously reported;

(v) A summary and analysis of all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or that the applicant is aware of, accompanied by a statement of any changes to the overall risk associated with the tobacco product, and a summary of any changes in the health risks, including the nature and frequency of the adverse experience, and potential risk factors;

(vi) A summary of sales and distribution of the tobacco product for the reporting period, to the extent that the applicant collects or receives such data, including:

(A) Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold;

(B) The Universal Product Code that corresponds to the product(s) identified in the PMTA; and

(C) Demographic characteristics of product(s) purchasers, such as age, gender, and tobacco use status;

(vii) Specimens of all labeling and descriptions of all labeling changes that have not been previously submitted under section 905(i) of the Federal Food, Drug, and Cosmetic Act, including the date the labeling was first disseminated and the date when dissemination was completely terminated;

(viii) Full color copies of all advertising for the tobacco product that has not been previously submitted, and the original date the materials were first disseminated and the date when their dissemination was completely terminated;

(ix) A description of the implementation of all advertising and marketing plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including a description of any:

(A) Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;

(B) Targeting of specific adult audiences by age-range(s), including young adults, ages 18 to 24, and other demographic or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;

(C) Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, or promotion;

(D) Use of owned, earned, shared, or paid social media to create labeling for, advertise, market, or promote the products;

(E) Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the products;

(F) Consumer engagements conducted by the applicant, on its behalf, or at its direction, including events at which the products were demonstrated; and

(G) Use of earned media or public-relations outreach to create labeling for, advertise, market, or promote the products;

(x) An analysis of the actual delivery of advertising impressions, by channel, by product (if applicable), and by audience demographics, including a breakout by age-group, that have not been previously submitted, verified against post-launch delivery-verification reports submitted to the applicant from an accredited source;

(xi) Additional information required to be reported under the terms of a marketing order (if applicable); and

(xii) An overall assessment of how the tobacco product continues to be appropriate for the protection of the public health.

(2) *Serious and unexpected adverse experience reporting*. The applicant must report all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or that the applicant is aware of to CTP's Office of Science through the Health and Human Services' Safety Reporting Portal or in another manner designated by FDA (if applicable) within 15 calendar days after the report is received by the applicant.

(b) *FDA review of postmarket reports*. (1) As part of its review of a postmarket report, FDA may require the applicant to submit additional information to enable it to determine whether a change results in a new tobacco product, or to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing order.

(2) FDA may notify an applicant that FDA has determined that a change described in a periodic report made under this section results in a new tobacco product outside the scope of the marketing order, requiring the submission of a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and issuance of a marketing order if the applicant seeks to market the new tobacco product, unless the new tobacco product can be legally marketed through a different premarket pathway.

Subpart E--Miscellaneous

§ 1114.45 Record retention.

(a) *Record retention by the applicant*. (1) Each applicant that receives a marketing order must maintain all records necessary to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing order, including records related to both the application and postmarket reports, and ensure that such records remain readily available to the Agency upon request. These records include, but are not limited to:

(i) All documents submitted to FDA as part of an application, periodic postmarket reports, and adverse experience reports;

(ii) All documentation demonstrating whether each:

(A) Nonclinical laboratory study was conducted in accordance with good laboratory practices that support the reliability of the results, such as the records described in part 58 of this chapter; and

(B) Clinical investigator has any financial conflicts of interest that may be a source of bias, such as the documentation described in part 54 of this chapter;

(iii) All other documents generated during the course of a study necessary to substantiate the study results, including:

(A) Communications related to the investigation between the investigator and the sponsor, the monitor, or FDA; and

(B) All source data for human subject and nonclinical investigations included in the application and postmarket reports, including records of each study subject's case history and exposure to tobacco products used in the investigation, including case report forms, progress notes, hospital records, clinical charts, X-rays, lab reports, and subject diaries; and

(iv) A list of each complaint, and a summary and analysis of all complaints, associated with the tobacco product reported to the applicant;

(2) These records must be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary. Documents that have been translated from another language into English (e.g., original study documents written in a language other than English) must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation.

(3) All records must be retained as follows:

(i) Records related to and including the PMTA must be retained for a period of at least 4 years from the date that the marketing order is issued.

(ii) Records related to postmarket reports, including both periodic and adverse experience reports, must be retained for a period of at least 4 years from the date the report was submitted to FDA or until FDA inspects the records, whichever occurs sooner.

(b) *Record retention by FDA*. FDA will retain information submitted to it in accordance with Federal Agency Records schedules and will provide a copy to persons to whom such information may legally be disclosed on request under the fee schedule in FDA's public information regulations in § 20.45 of this chapter.

§ 1114.47 Confidentiality.

(a) *General*. FDA will determine the public availability of any part of an application and other content related to such an application under this section and part 20 of this chapter.

(b) FDA shall routinely inform TPSAC of PMTA applications that have been submitted and afford the public the opportunity to comment on the need for referring particular PMTAs to TPSAC.

(c) *Confidentiality of data and information prior to an order*. Prior to issuing an order under this part:

(1) FDA will not publicly disclose the existence of an application unless:

(i) The applicant has publicly disclosed or acknowledged (as such disclosure is defined in § 20.81 of this chapter), or has authorized FDA in writing to publicly disclose or acknowledge, that the applicant has submitted an application to FDA; ~~**or**~~

(ii) FDA refers the application to TPSAC***;***

(iii)The applicant has submitted or concurrently submits a Modified Risk Tobacco Product (MRTP) application.

(2) FDA will not disclose the existence or contents of an FDA communication with an applicant regarding its application except to the extent that the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence

or contents of that particular FDA communication.

(3) Except as described in paragraph (b)(4) of this section, FDA will not disclose information contained in an application unless the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence of that particular information. If the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence of that particular information contained in an application, FDA may disclose the existence of that particular information.

(4) If FDA refers an application to TPSAC, the contents of the application will be available for public disclosure under part 20 of this chapter, except information that has been shown to fall within the exemption established for trade secrets and confidential commercial or financial information in § 20.61, or personal privacy in § 20.63.

(d) *Disclosure of data and information after issuance of a marketing order*. After FDA issues a marketing order, it may make the following information related to the application and order available for public disclosure upon request or at FDA's own initiative, including information from amendments to the application and FDA's reviews of the application:

(1) All data previously disclosed to the public, as such disclosure is defined in § 20.81 of this chapter;

(2) Any protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61 of this chapter;

(3) Information and data submitted to demonstrate that the new tobacco product is appropriate for the protection of public health, unless the information is shown to fall within the exemptions established in § 20.61 of this chapter for trade secrets and confidential commercial information, or in § 20.63 of this chapter for personal privacy;

(4) Correspondence between FDA and the applicant, including any requests FDA made for additional information and responses to such requests, and all written summaries of oral discussions between FDA and the applicant, unless it is shown to fall within the exemptions in § 20.61 of this chapter for trade secrets and confidential commercial information, or in § 20.63 of this chapter for personal privacy;

(5) In accordance with § 25.51(b) of this chapter, the environmental assessment or, if applicable, the claim for categorical exclusion from the requirement to submit an environmental assessment under part 25 of this chapter; and

(6) Information and data contained in postmarket reports submitted to FDA, unless the information is shown to fall within the exemptions established in § 20.61 of this chapter for trade secrets and confidential commercial information, or in § 20.63 of this chapter for personal privacy

(e) *Disclosure of data and information after the issuance of a no marketing order*. After FDA issues a no marketing order, FDA may make certain information related to the application and the order available for public disclosure upon request or at FDA's own initiative unless the information is otherwise exempt from disclosure under part 20 of this chapter. Information FDA may disclose includes, but is not limited to the tobacco product category (e.g., cigarette), tobacco product subcategory (e.g., filtered, combusted cigarette), package size, product quantity, characterizing flavor, and the basis for the no marketing order.

§ 1114.49 Electronic submission.

(a) *Electronic format requirement*. Applicants submitting any documents to the Agency under this part must provide all required information to FDA using the Agency's electronic system, except as provided in paragraph (b) of this section. The application and all supporting information must be in an electronic format that FDA can process, review, and archive.

(b) *Waivers from electronic format requirement*. An applicant may submit a written request, that is legible and in English, to the Center for Tobacco Products asking that FDA waive the requirement for electronic format and content. Waivers will be granted if use of electronic means is not reasonable for the applicant. To request a waiver, applicants can send the written request to the address included on our website (www.fda.gov/tobaccoproducts). The request must include the following information:

(1) The name and address of the applicant, a list of individuals authorized by the applicant to serve as the contact person, and contact information. If the applicant has submitted a PMTA previously, the regulatory correspondence should also include any identifying information about the previous submission.

(2) A statement that creation and/or submission of information in electronic format is not reasonable for the applicant, and an explanation of why creation and/or submission in electronic format is not reasonable. This statement must be signed by the applicant or by a representative who is authorized to make the declaration on behalf of the applicant.

(c) *Paper submission*. An applicant who has obtained a waiver from filing electronically must send a written application through the Document Control Center to the address provided in the FDA documentation granting the waiver.

Dated: July 24, 2019.

Norman E. Sharpless,

Acting Commissioner of Food and Drugs.

Dated: September 3, 2019.

Eric D. Hargan,

Deputy Secretary,

Department of Health and Human Services.

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