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Altria Client Services LLC (“ALCS”), on behalf of Nu Mark LLC (“Nu Mark”),\(^1\) submits these comments to the U.S. Food and Drug Administration (“FDA” or “the Agency”) in response to the above-captioned Federal Register notice (“Draft Guidance”) which outlines Premarket Tobacco Product Applications (“PMTA”) recommendations for Electronic Nicotine Delivery Systems (“ENDS”).

Congress intended to facilitate efforts to develop and market products with potentially less risk than conventional tobacco products when it empowered FDA to regulate tobacco products, including new tobacco products. ENDS are such innovative, potentially reduced harm products that advance this objective. The process envisioned by FDA’s Draft Guidance for the Agency’s authorization of PMTAs for ENDS products, however, may create roadblocks that run counter to the text and purpose of the Family Smoking Prevention and Tobacco Control Act (“FSPTCA”). If adopted in its current form, the Draft Guidance may result in many existing ENDS products being forced off the market and make it difficult for some manufacturers to develop new ENDS products. Should this occur, adult tobacco consumers will be deprived of important product choices.

Specifically, we are concerned that:

1) The Draft Guidance is not aligned to the FSPTCA’s goal of promoting public health because the complexity of information recommended for the application process and the short compliance period for FDA to complete PMTA reviews may result in some existing ENDS products being forced off the market.

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\(^1\) Nu Mark is a wholly-owned subsidiary of Altria Group, Inc. ALCS provides certain services, including regulatory affairs, to the Altria family of companies. “We” and “our” are used throughout to refer to Nu Mark, except where the context requires otherwise.

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2) The Draft Guidance does not include an accelerated or modified PMTA pathway for ENDS to provide flexibility and recognize ENDS' position on the tobacco risk continuum.

3) FDA’s expectations for data submissions to support a manufacturer’s PMTA for an ENDS product exceed the Agency’s statutory authority and the applicable regulatory framework, do not define key terms, and do not provide clarity regarding the PMTA approval process.

4) The Draft Guidance unreasonably limits meetings that manufacturers may seek with FDA regarding PMTAs for ENDS products.

I. Foundation: Congress’ Intent To Facilitate Tobacco Product Innovations That May Advance the Public Health

FDA’s authority to regulate tobacco products, including newly-deemed ENDS products, is grounded in the FSPTCA where Congress explicitly preserved a space in the market for tobacco products that adult tobacco consumers may use, subject to reasonable controls and appropriate regulatory oversight. Congress also recognized that this regulatory framework should foster innovation of tobacco products that may have overall benefits to public health. The resulting framework, therefore, was intended to acknowledge a substantial continuum of risk among tobacco products—including ENDS—and respect the right of adults to make informed choices about which, if any, tobacco products to use.

FDA has historically recognized that its regulation of new tobacco products should “spur innovation and help to create a market where available products are less dangerous when consumed, less likely to lead to initiation of tobacco use, and/or easier to quit.” FDA has also acknowledged the existence of a continuum of risk among nicotine and nicotine-related products, and that ENDS may have a positive impact on public health. In its Final Rule “Deeming Tobacco Products to be Subject to the Federal Food, Drug and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products” (“Deeming Rule”) FDA recognized “that the inhalation of nicotine (i.e., nicotine without the products of combustion) is of less risk to the user than the inhalation of nicotine delivered by smoke from combusted tobacco products.” In its Draft Guidance, however, FDA outlines a PMTA process for ENDS that is very burdensome and will impede harm reduction.

FDA is well aware that its PMTA process for ENDS will result in regulating a substantial percentage of ENDS products out of the market. Indeed, in the Final Regulatory Impact

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2 See FSPTCA § 3(7).
3 See, e.g., FSPTCA § 3(4).
7 81 Fed. Reg. at 28981.
Analysis for the Deeming Rule ("RIA"), FDA acknowledged that the Agency "expects a large share of ENDS products to exit rather than submit a premarket application" because only "one percent of ENDS devices may be grandfathered" and a substantial percentage will be subject to the PMTA process. Yet the RIA sets this admission aside and focuses on the notion that it will be relatively inexpensive to submit a PMTA. The assumptions on which FDA relies in calculating cost estimates are highly contingent on the availability of existing data that is tailored to the specifications of a particular ENDS product, on the specifications of the new tobacco product itself, and on the expectation that firms are able to bundle multiple products into a single PMTA submission. These assumptions, however, are directly at odds with the Draft Guidance which, as outlined below, sets forth new, onerous PMTA requirements that reach beyond the confines of Section 910 and what was contemplated in the RIA.

This is not the first time ALCS has addressed concerns with FDA’s PMTA guidances on behalf of Altria Group’s tobacco operating companies. In 2011, FDA issued its Draft Guidance for Industry: Applications for Premarket Review of New Tobacco Products. ALCS on behalf of Philip Morris USA (“PM USA”) and U.S. Smokeless Tobacco Co. (“USSTC”) in the December 2011 comments on that document, identified significant problems with FDA’s approach to regulating new tobacco products, including its arduous PMTA requirements, a lack of clarity and/or detail regarding certain terms or provisions in the draft guidance, and the belief that the PMTA review process, as drafted, was inconsistent with the FSPTCA’s stated purpose of encouraging innovation.

We also submitted comments in response to FDA’s Proposed Rule “Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products” (“Proposed Deeming Rule”). There again, we expressed concerns regarding FDA’s proposal to create considerable evidentiary requirements for PMTA applicants. We urged FDA to establish product pathways that reflect reasonable regulation, comply with the FSPTCA’s requirements, conform with congressional intent, and support manufacturers’ efforts to develop and bring to market innovative products that may advance the public health.

11 Id.
We continue to support FDA’s regulation of tobacco products, including those containing tobacco-derived nicotine. We recognize that not all ENDS products are of the same consistency and quality. For example, some electronic devices and flavors added to the liquid have been associated with harm. Such regulation, though, must allow industry participants to engage and compete in a dynamic market. To that end, we incorporate here the positions taken in previous comments to FDA submitted by ALCS on both the Proposed Deeming Rule and the PMTA process. Here we will focus on specific provisions of the Draft Guidance that have the very real risk of regulating many new ENDS products out of the market, which would be inconsistent with the FSPTCA and detrimental to adult tobacco consumers and the public health.

II. The Requirements and Deadlines for PMTA Submissions Could Result in the Removal of Many Existing ENDS Products from the Market

FDA’s Deeming Rule and the Draft Guidance together create an onerous PMTA process within a time frame that, as a practical matter, may be difficult for many ENDS product manufacturers to meet. Under the compliance policy established in the preamble to the Deeming Rule, the manufacturer of a currently-marketed ENDS product must file a PMTA for that product by August 8, 2018, or the product must be removed from the market. FDA’s expectation of receiving data from numerous clinical and nonclinical studies as described in the Draft Guidance may be difficult to include in a PMTA before this deadline except where such studies were begun before the publication of the Draft Guidance. The Draft Guidance and Deeming Rule, therefore, create a challenging barrier for many manufacturers.

Further, once the compliance period ends on August 8, 2018, and an applicant submits a PMTA, the statute requires the Agency to issue an order permitting or refusing to permit the marketing of the product within 180 days. Without regard to the statutory timelines, the Agency established in the Deeming Rule preamble a “12-month continued compliance period after [August 8, 2018] in which to obtain authorization from FDA,” which may not be sufficient time given the multitude of applications that FDA anticipates receiving. The preamble does establish, however, that if an “applicant has provided the needed information and review of a pending marketing application has made substantial progress toward completion, FDA may consider, on a case-by-case basis, whether to defer enforcement of the premarket authorization requirements for a reasonable time period.” The result is that many existing ENDS products may be removed from the market, either because the manufacturer could not generate the necessary data by the August 8, 2018, deadline or FDA failed to meet its deadline for authorizing the product and did not “defer enforcement . . . for a reasonable time period” under its challenging case-by-case scenario.

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14 See 81 Fed. Reg. at 28978.
16 81 Fed. Reg. at 28978.
17 81 Fed. Reg. at 29091 (FDA estimates the number of PMTAs it will receive annually is 750).
18 81 Fed. Reg. at 28978.
To avoid unnecessarily removing products from the market, FDA should allow currently marketed ENDS products to remain available to consumers for as long as it takes the Agency to issue an order permitting or prohibiting the marketing of a product. In other industries, the Agency has established reasonable, alternative frameworks for preapproval that promote the public health, and FDA should consider adopting comparable approaches to the PMTA process for the products at issue here.

For example, when FDA sought to evaluate the safety and effectiveness of over-the-counter ("OTC") drugs marketed in the United States before May 11, 1972, it established standards, or drug monographs, for OTC therapeutic drug classes.\(^{19}\) These monographs established conditions under which OTC drug products are generally recognized as safe and effective.\(^{20}\) While many monographs are still not finalized, FDA has allowed these OTC drug products to remain on the market while working to review and finalize the monographs.\(^{21}\)

FDA also took an alternative approach to unapproved prescription drugs that are currently available in the U.S. market. In 2011, FDA released a Compliance Policy Guide titled "Marketed New Drugs Without Approved NDAs and ANDAs,"\(^{22}\) which described the thousands of drug products that were marketed but not approved by the Agency, including drugs grandfathered under the Federal Food, Drug, and Cosmetic Act ("FDCA") in 1938, and drugs undergoing Drug Efficacy Study Implementation review. FDA developed a protocol to identify potential public health concerns and institute regulatory follow-up; it did not immediately remove these drugs from the market. As the Agency explained, this risk-based enforcement approach achieved its goals "without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market."\(^{23}\)

FDA should exercise similar restraint with ENDS products and allow them to remain on the market as an available alternative tobacco product for adult consumers, including current and former cigarette users, during the pendency of FDA’s PMTA reviews.

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\(^{19}\) 21 C.F.R. §§ 331-350.

\(^{20}\) Id.

\(^{21}\) Final monographs have been published for the majority of OTC drugs. Proposed monographs (designated as "tentative final monographs") have been issued for virtually all remaining OTC drug categories. FDA has taken the position that OTC drugs covered by ongoing OTC monograph proceedings may remain on the market, subject to current enforcement policies. See CPG Manual, Sec. 450.200 – General Provisions and Administrative Procedures for Recognition as Safe and Effective (CPG 7132b.15), available at www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg450-200.html; CPG Manual, Sec. 450.300 – General Provisions and Administrative Procedures for Recognition for Marketing Combination Products (CPG 7132b.16), available at www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg450-300.html.


\(^{23}\) Id.
III. FDA Should Modify the Draft Guidance to Implement an Accelerated or Modified PMTA Pathway for ENDS

To ensure that the Draft Guidance provisions, in practice, conform with Congressional intent and the FSPTCA’s stated objectives, we again encourage FDA to modify the Draft Guidance to implement an accelerated and/or modified PMTA process for ENDS products.

Section 910(c)(5)(B) specifically recognizes the differences between categories of tobacco products and that the information “sufficient to evaluate” whether a tobacco product is appropriate for the protection of the public health will differ depending on where the product falls on the risk continuum. FDA should, therefore, issue regulations identifying the specific evidentiary requirements and criteria that are sufficient to evaluate ENDS products—products that are lower on the risk continuum than conventional, combustible tobacco products. Such abbreviated requirements should reflect FDA’s determinations about what evidence is sufficient to demonstrate that an ENDS marketing authorization is “appropriate for the protection of the public health.”

To this end, FDA should simplify and streamline the PMTA process. It should establish baseline performance standards for ENDS products that, when met, would serve as the basis for an abbreviated or alternative marketing authorization pathway to satisfy the statutory PMTA requirements. The authority for such a performance standards-based approach is found in Section 907(a)(3), and FDA has the ability to request data from manufacturers to assist in creating these standards. If a manufacturer wishes to seek marketing authorization for a product with different or additional attributes not covered by applicable standards, FDA could utilize an abbreviated PMTA process to consider the novel attributes. Congress clearly intended that different levels of regulation would be appropriate for different categories of tobacco products. And FDA is sufficiently equipped to implement such accelerated or modified PMTA pathways for ENDS products. Indeed, FDA has similarly utilized this statutory authority in the past to develop flexible approval policies, modified processes, and non-enforcement policies for certain classes of drugs, medical devices, and other products. Consistent with these approaches to dealing with novel issues in other regulated industries, we continue to believe that FDA should employ such strategies to facilitate the PMTA process for ENDS as a means to foster important health goals, avoid impractical outcomes, encourage innovation of new products, and promote fairness and efficiency for ENDS which may be potentially less harmful than combustible tobacco products.

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standards system for ENDS, FDA could meet its public health obligations, which include ensuring potentially reduced risk products can get to market.\(^{27}\)

IV. FDA’s Requests in the Draft Guidance for Certain Types of Data are Unlawful, Unworkable, or Unrelated to Assessing Whether Marketing an ENDS is Appropriate for the Protection of Public Health

Section 910 of the FDCA establishes the contents of a PMTA and also the criteria by which FDA shall determine whether to authorize the marketing of the product that is the subject of a PMTA. The data necessary to meet the statutory PMTA content requirements are extensive but not limitless, and the Draft Guidance recommends the development and/or submission of information that goes beyond what was clearly contemplated by Congress.

Section 910(b)(1) of the FDCA requires a PMTA to include:

- full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of the tobacco product and whether it presents less risk than other tobacco products;
- a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of the tobacco product;
- a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, the tobacco product;
- adequate information to show that the tobacco product fully meets any applicable tobacco product standard under Section 907 or adequate information to justify any deviation from such standard;
- such samples of the tobacco product and of components thereof as the Secretary may reasonably require;
- specimens of proposed labeling for the tobacco product; and
- such other information relevant to the subject matter of the application as the Secretary may require.\(^{28}\)

Based on the contents of a PMTA “and any other information before the Secretary with respect to such tobacco product,” FDA shall authorize the marketing of a tobacco product if it finds that:

- well-controlled investigations, which may include one or more clinical investigations or other valid scientific evidence show that marketing the tobacco product would be appropriate for the protection of the public health;

\(^{27}\) Id. at 33-36.

- the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of the tobacco product conform to tobacco product manufacturing standards when they are established pursuant to Section 906(e);
- the proposed labeling is not false or misleading in any particular; and
- the tobacco product conforms in all respects to any applicable standard established under Section 907.29

Certain information requested by the Draft Guidance far exceeds this scope.

FDA also inappropriately uses this Draft Guidance as a vehicle to regulate by establishing the types of data it expects applicants to include in PMTAs for ENDS products. The way to impose data or submission requirements on applicants is through formal notice and comment rulemaking. Similarly, through the Draft Guidance, FDA is attempting to collect information for purposes beyond what it needs to make a decision about marketing authorization such as for future tobacco product standards, rulemaking, or guidances. The statutory data requirements for a PMTA are limited to that which Congress considered suitable to permit FDA to determine whether to authorize the marketing of a tobacco product pursuant to the criteria in Section 910(c) and not for purposes of assisting with FDA’s other regulatory objectives.

A. Section 910 Does Not Authorize FDA to Require Comparisons to Other Products in the Same Category as Part of a PMTA Review

FDA expects that ENDS PMTAs include comparison data to other products within the same category. As one example, the Draft Guidance recommends information on “the relative health risks of the new tobacco product for both users and nonusers compared to other tobacco products on the market (e.g., other ENDS, combusted tobacco products such as cigarettes), as it may be expected that consumers of current products within the same category may switch to using a newly marketed product.”30

Congress did not intend that FDA seek and consider information comparing the product under review in a PMTA to other products in the same category—in this case comparing an ENDS product to other ENDS products. Section 910(b)(1)(A), which provides the statutory authority for the Draft Guidance, expressly requires that a PMTA include reports of information “concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products.”31 Interpreting “other tobacco products” in this section to include other ENDS products defeats Congress’ intent that the “appropriate for the protection of public health”

30 Draft Guidance at lines 895-99. FDA also recommends that ENDS PMTAs include data comparing the product’s properties to other marketed tobacco products in the same category. Id. at lines 1087-95.
standard would ensure that new tobacco products for which FDA issues marketing authorization orders “do not introduce more risk than conventional tobacco products.”

FDA should remove the references to recommending that PMTA applicants include comparative information on other ENDS products in the final guidance.

B. Section 911 Data Requirements Cannot be Conflated with the More Limited Section 910 Data Requirements

Congress established specific limited data requirements for marketing authorization of a new tobacco product under the PMTA provisions. Congress also established more robust data requirements for authorization to market a product with a modified risk claim under the modified risk tobacco product (“MRTP”) application provisions. ENDS may be an entire class of tobacco products that pose lower risk to individuals or the population as a whole or both. Even if this is the case, however, the statutory data requirements for authorization to market a product with a modified risk claim cannot be superimposed on the PMTA process.

1. Section 910 Does Not Authorize FDA to Require Data Regarding the Likelihood of Using an ENDS Product Instead of a Tobacco Cessation Product as Part of a PMTA Review

Congress did not authorize FDA to request or consider research regarding whether consumers will switch to the new tobacco product, here an ENDS product, instead of switching to an FDA-approved product for tobacco cessation as part of a PMTA review. Yet, the Draft Guidance includes a request for that information. Only in Section 911, which governs MRTPs, did Congress include the additional mandate that FDA take into account the risks and benefits to persons from the use of a tobacco product compared to the use of smoking cessation products approved by FDA to treat nicotine dependence. Had Congress intended FDA to consider data comparing tobacco products to FDA-approved tobacco cessation products when making marketing authorization determinations for PMTAs, it would have explicitly included a requirement in Section 910, just as it did in Section 911.

FDA should remove recommendations that PMTA applicants include research about consumers switching to the new ENDS product instead of switching to an FDA-approved product for tobacco cessation from the final guidance.

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32 S. Rep. No. 105-180, at 23 (1998) (stating that “Section 910...provides the Secretary with authority to obtain needed data on the risks of novel tobacco products, and to assure that such products do not introduce more risks than conventional tobacco products.”) (emphasis added).

33 If FDA refuses to delete references to submitting comparative information on other ENDS products in the final guidance, it should include criteria for selecting "other similar products within the same category." As an example, comparisons to products that are too similar, such as products with very similar designs, may prove to be of very limited value. The lack of criteria will likely create inefficiencies and demand for additional meetings with FDA to learn whether the “similar product” in the same category selected by an applicant is appropriate.

34 Draft Guidance at lines 1389-1420.

2. **Section 910 Does Not Authorize FDA to Require Consumer Perception Studies and Labeling Comprehension Studies as Part of a PMTA Review**

The Draft Guidance requests that applicants include "consumer perception evaluations" of the labeling and packaging and "studies demonstrating that users and nonusers understand the product's labeling and instructions for use."\(^{36}\) Section 910 does not include a requirement for applicants to submit this information in PMTAs. In contrast, Section 911 requires applicants to submit results of consumer perception testing on the product's label and marketing materials.\(^{37}\) Had Congress intended FDA to consider consumer perception and comprehension data when making marketing authorization determinations for PMTAs, it would have explicitly included a requirement in Section 910, just as it did in Section 911.

FDA should remove recommendations that PMTA applicants include consumer perception and comprehension data from the final guidance.

**C. Section 910 Does Not Authorize FDA to Require Information on Known Problems with Previous or Similar Versions of the Product as Part of a PMTA Review**

Contrary to FDA's statutory authorization, the Draft Guidance recommends that applicants provide information describing "the conditions for using the product or instructions for use, as part of the full statement of the principle or principles of operation required by 910(b)(1)(B), and if known, problems with use in previous or similar versions of the new product."\(^{38}\) Information on such other versions of the product is not contemplated by the FSPTCA and falls outside the Agency's statutory authority.

Section 910(b)(1)(B) requires "a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product."\(^{39}\) The phrase "such tobacco product" refers to the particular product(s) being evaluated. The FDCA does not give FDA the authority to request this information on previous or similar versions of the product. The Draft Guidance appears to recognize this distinction, first requiring the information under 910(b)(1)(B), and using the word "and" after the statutory citation to include the other types of products.

In addition, information on such other products is not pertinent to the PMTA for the product(s) at issue and could lead to the submission of data tainted by a design or manufacturing feature that has been corrected. A product's effects on the public health can be determined based on the data about that product in its current form.

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\(^{36}\) Draft Guidance at lines 1422-33, 1495-1500.


\(^{38}\) Draft Guidance at lines 773-75 (emphasis added).

FDA should remove recommendations that PMTA applicants include data on previous or similar versions of the product from the final guidance.

D. Neither Section 910 Nor the FSPTCA Authorize FDA to Require Information on Sources of Funding for Nonclinical and Human Subject Studies as Part of a PMTA Review

The Draft Guidance recommends that applicants provide "to the extent the information is available . . . the source of funding for all studies and provide a statement regarding any potential financial conflicts of interest." The FSPTCA, however, provides no statutory authority for FDA to collect this information, particularly as part of a PMTA under Section 910.

The FSPTCA, in Section 904, references the submission of financial information only in the context of documents relating to marketing research involving the use of tobacco products or marketing practices and the effectiveness of such practices used by tobacco manufacturers and distributors. The FSPTCA contains no requirements related to the submission of statements of financial conflicts of interest at all much less in the context of PMTAs.

FDA should remove recommendations that PMTA applicants provide information about funding sources and potential conflicts of interest for studies in the application from the final guidance.

E. Neither Section 910 Nor the FSPTCA Authorize FDA to Require Research on the Appeal of and Use Intentions of ENDS Product Flavors as Part of a PMTA Review

The Draft Guidance cites to Section 910(b)(1)(A) in recommending that ENDS PMTAs contain research on flavor development testing and consumer perceptions for appeal and use intentions based on labeling, flavoring, and product design. FDA is attempting to stretch statutory authority that requires the production of known or knowable data demonstrating the health risks of new tobacco products to also mean that PMTA applicants must demonstrate that their product presents less "risk" of appeal to children and adults, especially as it relates to flavors. The FSPTCA, however, does not require studies on product and label appeal. FDA's attempt to expand the statute's request for data to include data on the "risk" of appeal of flavored products to new users goes beyond the statutory authority in Section 910(b)(1)(A).

FDA's recommendation that data related to appeal of flavors be included in ENDS PMTAs, therefore, appears to be an attempt to force manufacturers to provide data that could serve as supporting data for future regulatory standards. To the extent FDA intends to consider or adopt additional product standards for flavors, it should request information from manufacturers consistent with the procedures set forth in Section 907. Until then, FDA should remove its recommendations.
recommendation for applicants to include data related to product and label appeal in PMTAs from the final guidance.

F. Neither Section 910 Nor the FSPTCA Authorize FDA to Require Research on Abuse Liability, Addictiveness, and Attractiveness Data as Part of a PMTA Review

In several places the Draft Guidance recommends testing of abuse liability, addictiveness, and attractiveness of the new tobacco product. The Draft Guidance, though, lacks clear definitions for what FDA expects applicants to study. Also, these recommendations fall outside the scope of the FSPTCA as Congress showed no intent to require such information in PMTAs. In Section 910, Congress provided specific requirements related to testing and data for applicants to follow in submitting PMTAs. Notably, data gathered from testing of abuse liability, addictiveness, and attractiveness are not included in Section 910, nor are those terms found anywhere within the text of the FSPTCA. FDA should remove its recommendation for applicants to include testing data related to abuse liability, addictiveness, and attractiveness in PMTAs from the final guidance.

G. Section 910 Does Not Authorize FDA to Require Certain Marketing and Manufacturing Data Requested by FDA as Part of a PMTA Review

The Draft Guidance recommends that manufacturers submit a marketing plan and narrative descriptions, accompanied by a list and summary of all standard operating procedures ("SOPs") for various manufacturing processes, supply chain issues, and complaint handling as part of the PMTA.

FDA’s request for such commercial information: (1) is outside the scope of the requirements for a PMTA in Section 910; (2) could encompass a wide variety of far-reaching and complex commercial documents that have no bearing on whether marketing an ENDS product would be appropriate for the protection of public health; (3) is unnecessarily burdensome; and (4) may lead the Agency to make subjective and unpredictable determinations. Moreover, there is no legal or statutory requirement or industry guidance for any FDA-regulated product that places similar recommendations on manufacturers to submit SOPs and commercial marketing plans as part of a product premarket analysis. These considerations support removal or significant narrowing of the data requests in the Draft Guidance. The requests are not authorized by Section 910 or any other provision of the FSPTCA, and courts have held that FDA cannot create records-access authority under FDCA § 701(a)’s general authorization “to promulgate regulations for the efficient enforcement of the Act.”

With respect specifically to certain requested manufacturing information, FDA improperly uses the PMTA process as a vehicle to require certain manufacturing methods and controls on topics such as hazard analysis and validation and verification activities. The proper vehicle, however, for imposing such requirements is through notice and comment rulemaking as provided for in

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44 Id. at lines 916-17, 1520-22, 1594-97.
45 Id. at lines 1134-60, 1479.
Section 906(e). \footnote{21 U.S.C. § 387(f)(1)(A) (stating the Secretary shall promulgate “regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, preproduction design validation (including a process to assess the performance of a tobacco product), packing, and storage of a tobacco product conform to current good manufacturing practice, or hazard analysis and critical control point methodology, as prescribed in such regulations...”).} Further, some of the information requested in the Draft Guidance appears to improperly impose product standards in areas such as compliance with voluntary standards. The statutory authority to establish tobacco product standards is in Section 907 through notice and comment rulemaking.

In this instance, we urge FDA to adopt a standard that is consistent with the regulatory framework centered on appropriate well-controlled investigations and valid scientific evidence. Accordingly, we recommend that the submission of SOP-related information and a marketing plan as a part of the PMTA be deleted from the final guidance.

V. FDA Should Revise Provisions That are Inconsistent with Its Statutory Authority, Define Key Terms, and Clarify the Approval Process

A. FDA Should Clarify Whether Certain Products Require Nicotine Exposure Warnings and Child-Resistant Packaging

FDA recommends the inclusion of a nicotine exposure warning \footnote{Draft Guidance at lines 549-56.} on finished ENDS products, as well as child-resistant packaging. \footnote{Id. at lines 617-26.} In making these recommendations, the Draft Guidance does not differentiate between types of ENDS products, namely whether the product is an open (consumer has access to liquid nicotine) or closed (consumer cannot access the liquid nicotine) system and whether safety features already incorporated into the product obviate the need for certain warnings or specific child-resistant packaging. This failure to differentiate among product types in proposing commercial speech (labeling) and packaging regulations is inconsistent with procedural and statutory requirements, and raises concerns under the First and Fifth Amendments. To the extent labeling requirements are properly addressed in a guidance at all (as opposed to an appropriately tailored rulemaking), FDA should revise the Draft Guidance to avoid these concerns. \footnote{Agencies must evaluate the compliance costs associated with proposed regulatory actions, weigh those costs against anticipated benefits, and consider reasonable alternatives. See Executive Order No. 12866, 58 Fed. Reg. 51735 (Oct. 4, 1993).}

As previously stated in our comments to FDA’s Advance Notice of Proposed Rulemaking “Nicotine Exposure Warnings and Child-Resistant Packaging for Liquid Nicotine, Nicotine-Containing E-Liquid(s), and Other Tobacco Products” \footnote{80 Fed. Reg. 37555 (July 1, 2015).} science and evidence demonstrates that the potential likelihood of exposure to an acutely toxic dose of nicotine is low for ENDS products with closed cartridges. \footnote{See Letter from James E. Dillard III to Docket No. FDA–2015–N–1514 (80 Fed. Reg. 37555 (July 1, 2015)) – Comments on Advance Notice of Proposed Rulemaking “Nicotine Exposure Warnings and Child-Resistant
packaging and nicotine exposure warnings are not warranted for such ENDS products. Nu Mark currently manufactures closed-container systems where the disposable nicotine cartridges ("cartomizers") are sold pre-filled and are not designed to be refilled. Nu Mark's current cartomizers are designed to be inaccessible and not openable.

ALCS agrees with FDA that a nicotine exposure warning and child-resistant packaging are appropriate and promote public health when applied to open-container systems, e-liquid vials, and closed-container systems that are not designed to be inaccessible and not openable. The warning and child-resistant packaging are unnecessary for Nu Mark's current cartomizers as the risk of nicotine exposure has been mitigated through other means, as has the risk to public health. There is no public health reason for requiring a nicotine exposure warning or child-resistant packaging for these products.

FDA must refrain from actions that arbitrarily or capriciously restrict manufacturers' ability to continue marketing their existing products or bring new products to market, and from imposing regulatory burdens that are contrary to law. The Draft Guidance contravenes these principles by subjecting closed-container products to compelled speech and packaging restrictions that FDA has not adequately tied to any legitimate regulatory objective under the FSPTCA, and that FDA would impose without adequate notice or consideration of First Amendment and other burdens.53

These threshold procedural problems with the labeling provisions in the Draft Guidance are amplified by substantive First Amendment concerns because the Draft Guidance does not articulate a legitimate government interest in applying the suggested disclosures to closed containers, much less articulate a "reasonable fit between the particular means chosen and the government interest pursued."54 Even the most forgiving standard of First Amendment review would require FDA to identify a legitimate "government interest" in applying the proposed labeling content to closed containers, and to show that the required disclosures would be "purely factual" and "reasonably related" to that government interest.55 The Draft Guidance does not do so, and certainly does not satisfy the more demanding (Central Hudson56) standard of First Amendment scrutiny the D.C. Circuit recently held applicable to compelled (as opposed to voluntary) commercial disclosures.57

Packaging for Liquid Nicotine, Nicotine-Containing E-Liquid(s), and Other Tobacco Products" (September 30, 2011).


54 See POM Wonderful, LLC v. FTC, 777 F.3d 478, 502 (D.C. Cir. 2015) (internal quotation marks omitted).


56 See Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n, 447 U.S. 557, 566 (1980) (a burden upon commercial speech may only survive if the government can affirmatively prove that (1) the asserted interest is substantial, (2) the restriction directly and materially advances the interest, and (3) the restriction is narrowly tailored).

57 Nat’l Ass’n of Mfrs. v. SEC, 800 F.3d 518, 530 (D.C. Cir. 2015).
The labeling provisions in the Draft Guidance also raise due process and regulatory takings concerns under the Fifth Amendment to the extent failure to comply with the provisions could result in removal of ENDS products from the market.

FDA can and should avoid all of these problems with the labeling and packaging provisions by removing them from the final guidance, at least with respect to closed-container products.

B. FDA Lacks Authority to Conduct Inspections of Tobacco Product Research Sites

The Draft Guidance indicates that FDA plans to inspect clinical and nonclinical research sites to support the Agency’s review of PMTAs for ENDS products, without referencing any supporting statutory or regulatory provisions.\(^\text{58}\) The Agency has made no such statement in any other guidance regarding its PMTA authorities.\(^\text{59}\) Further, FDA has not promulgated any regulations regarding investigational tobacco products or its access to related research data, as specified by Sections 910(g) and 704 of the FDCA.\(^\text{60}\) Indeed, with respect to tobacco products, Section 704 states that no FDA inspection shall extend to research data “other than data relating to new . . . tobacco products and subject to reporting and inspection under regulations lawfully issued pursuant to . . . chapter IX;” however, FDA has issued no such regulations.

The Agency has not set forth its authority or procedures for inspecting research sites that study tobacco products for purposes of collecting data for PMTAs, including the research data available at such sites, as it has done for other products subject to FDA premarket review.\(^\text{61}\) While the Agency has issued regulations for good laboratory practice (GLP) for nonclinical laboratory studies, codified at 21 C.F.R. part 58, as well as rules governing the protection of human subjects, codified at 21 C.F.R. part 50, these regulations do not apply by their terms to tobacco products.\(^\text{62}\) Moreover, when FDA issued a direct final rule amending its general regulations to include tobacco products after the enactment of the FSPTCA, it did not amend these regulations to apply to tobacco products.\(^\text{63}\)

FDA lacks authority to inspect clinical and nonclinical research sites to support its review of PMTAs for ENDS products. FDA’s performance of such inspections absent any notice of the requirements would therefore raise due process and APA concerns.

\(^{58}\) Draft Guidance at lines 416-19.


\(^{60}\) 21 U.S.C. §§ 387j, 374.

\(^{61}\) See 21 C.F.R. §§ 312.68, 812.145.

\(^{62}\) See 21 C.F.R. §§ 58.1, 50.1.

\(^{63}\) See 75 Fed. Reg. 73951 (Nov. 30, 2010).
C. Premarket Product Assessments Can Provide Only Estimates of Postmarket Outcomes

The Draft Guidance reiterates language from the FDCA stating FDA will deny PMTAs where it finds “there is a lack of showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health.” The Agency should clarify that there are inherent uncertainties regarding post-market or population outcomes and that premarket testing of a new tobacco product is not deficient when it cannot quantify absolute post-market or population outcomes.

The final guidance should also acknowledge that premarket data may not definitively “disprove” increased initiation or decreased cessation of tobacco products and that the lack of such definitive data will not lead FDA to find that an applicant has failed to show the product is appropriate for the protection of the public health. An applicant can only measure the likelihood of increased initiation or decreased cessation through reliable scientific studies of actual tobacco use prevalence once it markets a new tobacco product. Importantly, if FDA observes unacceptable outcomes related to a new tobacco product, the Agency can order its removal from the market under Section 910(d), which authorizes FDA to “issue an order withdrawing the [new product marketing authorization] order if the Secretary finds (A) that the continued marketing of such tobacco product no longer is appropriate for the protection of public health.”

The final guidance should clarify that FDA will not deny a marketing authorization for lack of absolute post-market or population outcomes in a PMTA when effective measures can be taken after a product is on the market to address any such concerns.

D. Certain Terms in the Draft Guidance Lack Definition and Clarity

The Draft Guidance provides a collective definition for terms which are separately defined by statute and/or regulation. Section 910(b)(1)(B) provides that a PMTA shall contain “a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product.” In reference to this requirement, the Draft Guidance defines “components, ingredients and additives,” collectively, to “include anything, other than accessories, that may reasonably be expected to directly or indirectly become part of, or affect the characteristics of, the finished new tobacco product (including, but not limited to, liquid reservoirs, solvents, flavor additives, heating coils, batteries, and pH modifiers).”

“Additive”, however, is already a stand-alone, statutorily-defined term. Section 900(1) defines “additive” as:

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...

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64 Draft Guidance at lines 437-39.
67 Draft Guidance at lines 975-78.
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. 68

Similarly, the Deeming Rule provides a stand-alone definition for “components or parts” as “any software or assembly of materials intended or reasonably expected: (1) To alter or affect the tobacco product’s performance, composition, constituents, or characteristics; or (2) To be used with or for the human consumption of a tobacco product. Component or part excludes anything that is an accessory of a tobacco product.” 69

The final guidance should omit a collective definition of “components, ingredients and additives” and use the relevant individual definitions in the statute and implementing regulations.

E. The Requested Labeling Information is Inconsistent with the FDCA

The discussion of “labeling” under Section 201(m) of the FDCA should be revised in the final guidance (Section VI.E) for consistency with that statutory provision. The final guidance should change the phrase “and includes labels, inserts/onserts, instructions, and other accompanying information or materials” to “and includes labels and other written, printed, or graphic matter accompanying the product.”

Otherwise, the Draft Guidance might suggest that a PMTA must include items that Congress did not specify in Section 910 and that the statute expressly regulates under other provisions.

F. The Requested Manufacturing Information Will Require Additional Agency Action

Pursuant to Section 910(b)(1)(C), a PMTA must include a full description of methods of manufacturing and processing, which the Draft Guidance recommends should include “a listing of all manufacturing, packaging, and control sites for the product, including the facility name and address, and a contact name and telephone number for each facility.” 70 Alternatively, an applicant may state that it is not submitting the information in a PMTA and explain why. The Draft Guidance also recommends that a PMTA provide seven categories of information 71 that cover many aspects of manufacturing that the Agency ordinarily would address in regulations. 72

FDA should promulgate regulations addressing those seven categories. Until it does so, FDA lacks statutory authority to expect applicants to submit information in categories beyond “the

70 See Draft Guidance at lines 1128-38.
71 Id. at lines 1140-1156.
methods used in, and the facilities and controls used for the manufacture of products subject to PMTAs.\textsuperscript{73}

The final guidance also should recognize that applicants, in advance of PMTA authorization, are not likely to have sufficiently scaled-up manufacturing to enable complete submissions on these issues.

G. The Draft Guidance Does Not Provide Sufficient Information About the PMTA Review Process

The Draft Guidance, in describing the Agency’s procedure for reviewing PMTAs, provides insufficient information in several respects.

First, the Agency should promulgate regulations to clarify key process elements of the PMTA review. Section IV.C. of the Draft Guidance provides inadequate guidance concerning the steps, procedures, and milestones as well as the relative timing of each, that FDA will utilize to evaluate PMTAs “as promptly as possible” within the 180-day statutory deadline, including communicating with the applicant. As it has in other contexts, FDA should, after notice and comment, issue a regulation that clarifies such issues as initial filing review, the identification and notice to the applicant of application deficiencies, options for curing any such deficiencies or amending the application, and the timing and effect of such steps on the statutory review period.\textsuperscript{74} Regulations also should address such topics as dispute resolution, the need and opportunity for hearings, and judicial review.\textsuperscript{75}

Second, FDA should establish channels of communication with applicants during the course of ENDS PMTA review. If FDA determines during review that additional clinical and/or nonclinical studies may be required to demonstrate the health risks of the ENDS product, FDA should communicate this information to the applicant and provide adequate time to respond to such a preliminary finding rather than denying an application outright. In addition, when FDA is reviewing the application of a currently marketed ENDS product and determines additional clinical and/or nonclinical studies may be required, the Agency should allow the ENDS product to remain on the market while communicating this information to the applicant. This approach is consistent with the preamble to the Deeming Rule which allows FDA to consider “defer[ing] enforcement of the premarket authorization requirements for a reasonable time period.”\textsuperscript{76} The final guidance should establish these channels of communication with applicants during ENDS PMTA review and reaffirm the Agency’s position with respect to its enforcement discretion.

Third, the final guidance should address procedures for denied PMTAs. In the event of a denial, Section 910(c)(3) requires FDA to inform the person submitting a PMTA of “the

\textsuperscript{73} 21 U.S.C. § 387j(b)(1)(C).
\textsuperscript{74} 21 C.F.R. §§ 314.101, 314.60-314.71, 314.100 (filing review, amendments, supplementation, resubmission, and time frame for substantive review).
\textsuperscript{75} 21 C.F.R. §§ 314.200, 314.201, 314.235 (hearing procedures and judicial review).
\textsuperscript{76} 81 Fed. Reg. at 28978.
measures required to remove such application from deniable form." The final guidance should reflect that statutory requirement, specifying how the applicant may reverse a denial. Moreover, an order denying authorization under Section 910 would entitle the applicant to judicial review under Section 912 of the FDCA. To facilitate resolution of disputes relating to denial decisions, FDA should explain any procedures that it will make available to resolve disputed denials pursuant to 21 C.F.R. § 10.75. In the final guidance, FDA should also describe the process(es) that it intends for applicants to use to obtain review of disputes arising during the review of a PMTA.

H. FDA Should Issue Regulations Under Section 910(g) for Investigational Tobacco Products

In the Draft Guidance, FDA requests that applicants meet with FDA to review their investigational plan for use of investigational tobacco products. As set forth in PM USA’s and USSTC’s comments on Draft Guidance for Industry and Investigators: Use of Investigational Tobacco Products, FDA must engage in notice and comment rulemaking to create an entirely new regulatory framework for investigational tobacco products. Moreover, Section 910(g) authorizes FDA to promulgate regulations establishing an investigational exemption from the premarket requirements for new tobacco products. Nu Mark incorporates PM USA’s and USSTC’s comments to that docket here.

I. Protecting a Product through the Distribution System Does Not Render That Packaging a “Component, Ingredient, or Additive”

The Draft Guidance recommends that ENDS PMTAs include detailed information regarding the product’s container closure system, which “refers to the packaging components that contain and protect a tobacco product, even if they are not in direct contact with the tobacco product, but are intended to provide protection to the product as it moves through the distribution system.” FDA’s definition of packaging as a “component, ingredient, or additive” solely because that packaging is designed to protect a product during transport is inconsistent with the Draft Guidance’s definition, the regulatory definitions, and the purpose of the FSPTCA to promote public health.

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78 Cf 21 C.F.R § 314.110 (complete response letters).
82 If by this statement FDA is assuming that all packaging that is in direct contact with a tobacco product becomes a component or part of a tobacco product, it is making an improper assumption.
83 Draft Guidance at lines 979-82.
The Draft Guidance defines “component, ingredient, or additive” to “include anything, other than accessories, that may reasonably be expected to directly or indirectly become part of, or affect the characteristics of, the finished new tobacco product.” FDA then provides the example of a container holding an e-liquid. FDA states the container could “affect or alter the performance, composition, constituents, or characteristics of a tobacco product . . . [by] leach[ing] ingredients from the packaging into the product.” Packaging that is not in direct contact with the tobacco product and is designed only to protect a product during transport does not fall within the definition of a “component, ingredient, or additive” because it would not affect the characteristics of the finished tobacco product, and FDA’s example is particularly illustrative of that point. Indeed, there would not be a concern of leaching from the packaging when the packaging is not in direct contact with the tobacco product.

J. Certain HPHC Testing Required by the Draft Guidance are Unrelated to Determining Whether an ENDS Product Is Appropriate for the Protection of Public Health

As set forth in Nu Mark’s comments to the Proposed Deeming Rule, which we incorporate here, meaningful testing for harmful and potentially harmful constituents (HPHCs) requires a category specific list of constituents, testing protocols, validated consensus standards and certified reference products to appropriately evaluate (in conjunction with other information) whether an ENDS product is appropriate for the protection of public health. The Draft Guidance acknowledges that FDA intends to establish a list of HPHCs “that includes HPHCs in ENDS products . . .” The Draft Guidance does not mention intentions regarding testing protocols, validated consensus standards and certified reference products. FDA should revise the final guidance so that HPHC testing is required only after FDA develops a category-specific HPHC list for ENDS products, establishes protocols and validated consensus standards, utilizes certified reference materials to ensure the integrity of the data sought, and implements laboratory proficiency testing.

Additionally, the Draft Guidance makes very specific recommendations for testing ENDS products that are not necessary. Specifically, the final guidance should be revised regarding the number of replicates, specific constituents to measure, and the inclusion of both “non-intense” and “intense” aerosol collection regimes. The number of replicates should be determined based upon reproducibility of the products. Some products may require more replicates than others due to manufacturing control and this should be demonstrated in the data provided to the Agency. As to the appropriate HPHCs for testing, many of the constituents identified in the Draft Guidance result from combustion of tobacco and are not relevant to products like ENDS that do not burn tobacco. Constituents that result only from combustion of tobacco will not be detected in ENDS aerosols. Finally, “intense” aerosol collection regimes are sufficient to demonstrate the potential maximum exposure. “Non-intense” aerosol collection regimes are repetitive to “intense” aerosol collection regimes because they will simply show lower concentrations of aerosol components and constituents. While applicants should demonstrate concentrations of

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84 Id. at lines 975-77.
85 Id. at lines 982-87.
86 See Draft Guidance at note 28.
constituents in ENDS aerosols, “intense” aerosol regimes are sufficient to demonstrate the potential maximum exposure.

VI. FDA Should Encourage, Not Artificially Limit, Dialogue with Applicants

Throughout the Draft Guidance, FDA sets forth its commitment “to helping industry better understand the tobacco product review process and the requirements of the law.” To that end, the Draft Guidance encourages industry to meet with FDA to discuss a variety of topics, including (1) the development of a PMTA and the premarket review process; (2) how best to prepare a product application; (3) alternatives to well-controlled investigations that an applicant wishes to use; (4) plans for use of investigational tobacco products; (5) what, if any, animal testing is appropriate; and (6) plans to conduct computational modeling. Yet, Section XII of the Draft Guidance states that “CTP intends to grant no more than one or two meetings per applicant.”

A cap on the number of meetings per applicant is inconsistent with the FSPTCA’s goal of promoting less harmful tobacco products, particularly when the Agency has established deadlines that must be met for such a product to remain available on the U.S. market. Proportional and reasonable access to, and appropriate contact between, the Agency and manufacturers will lead to optimized product development and timely product reviews. FDA should, therefore, clarify that, while one to two meetings may be the initial guideline, the Agency will be open to taking additional meetings when and as appropriate, and will further provide for informal interactions which may include phone calls or email exchanges directly with FDA staff during the review process.

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87 See Draft Guidance at lines 38-42 (“FDA is committed to helping industry better understand the tobacco product review process and the requirements of the law and will continue holding public Webinars and meetings with industry in order to assist manufacturers of newly deemed tobacco products. FDA also has published guidance on meetings with industry; this has enabled FDA to have many productive meetings to address companies’ specific questions on their development of tobacco products.”); lines 124-28 (“If an applicant wishes to discuss the development of a product application, the applicant may request a meeting with FDA as described in section XII of this document and further discussed in FDA’s final guidance, Meetings with Industry and Investigators on the Research and Development of Tobacco Products.”); lines 314-16 (“FDA has taken several steps to assist manufacturers and industry to better understand the tobacco product premarket review process and the FD&C Act’s statutory requirements, including: (1) Encouraging meetings between CTP and the applicant;”; lines 336-39 (“If an applicant wishes to discuss its development of a PMTA, the applicant may request a meeting as set forth in FDA’s final guidance, Meetings with Industry and Investigators on the Research and Development of Tobacco Products.”); lines 366-68 (“If an applicant wishes to discuss how best to prepare a product application, the applicant may request a meeting as set forth in FDA’s final guidance, Meetings with Industry and Investigators on the Research and Development of Tobacco Products.”); lines 470-73 & 998-1001 (“If an applicant has questions or other alternatives to well-controlled investigations it would like to utilize, we recommend that the applicant meet with FDA to discuss the approach prior to preparing and submitting an application.”); lines 1204-09 (“FDA encourages persons who would like to study their new tobacco product to meet with the Office of Science in CTP to discuss their investigational plan. The request for a meeting should be sent in writing to the Director of CTP’s Office of Science and should include adequate information for FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss agenda items.”); lines 1348-50 (“FDA encourages sponsors to meet with CTP early in the development process to discuss what, if any, animal testing is appropriate and the suitability and acceptability of non-animal tests for their particular new tobacco product.”).

88 See id. at lines 1968-72 (emphasis added).
Moreover, if the one to two meeting limit remains in the final guidance, FDA should clarify that the number of meetings per applicant is per application as well. Certainly if an applicant submits more than one PMTA, the applicant is permitted to meet with FDA at least one to two times per application as each ENDS application may present different issues. FDA, therefore, should clarify that one to two meetings per applicant is simply an initial goal for each application and that FDA will evaluate additional requests for meetings for each application on a case-by-case basis.

**Conclusion**

We appreciate the opportunity to submit these comments. As FDA finalizes its Draft Guidance, we urge the Agency to continue to develop tobacco regulations and guidance based on science and evidence, and to further support manufacturers’ efforts to develop and bring to market innovative, potentially reduced risk products. Considering alternatives such as an accelerated or modified PMTA pathway for ENDS is consistent with this approach. FDA also should revise the final guidance to be clear and consistent with the FDCA. As always, we would be happy to discuss these comments.

Sincerely,

[Signature]