SMARTT
COALITION

March 23, 2017

Caryn Cohen, M.S.
Office of Science
Center for Tobacco Products
U.S. Food and Drug Administration
Document Control Center
Bldg. 71, Rm. G335
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Docket No. FDA–2017–N–0001: Tobacco Products Scientific Advisory Committee; Notice of Meeting

---

Dear Ms. Cohen:

The Small Manufacturers Association for the Reasonable Treatment of Tobacco Coalition ("SMARTT") submits the following comments to the above-referenced docket. SMARTT is a coalition of Subsequent Participating Manufacturers to the multi-state Master Settlement Agreement ("MSA") who have issues of common concern with respect to the implementation of the Federal Food, Drug, and Cosmetic Act ("FDCA" or "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act").

SMARTT appreciates the opportunity to submit the following comments to the U.S. Food and Drug Administration ("FDA") Center for Tobacco Products ("CTP") related to the upcoming April 6, 2017 meeting of the Tobacco Products Scientific Advisory Committee ("TSPAC" or the "Committee"). The meeting notice states, "[t]opics will include the statutory standards applicable to the different types of applications, the scientific basis for review decisions, with a focus on PMTA and MRTPA, and the role of the committee in the review process."[1] Our comments make the following points regarding these issues:

- FDA must ensure that TPSAC members apply an appropriate standard for review of the scientific evidence provided in support of a PMTA or MRTPA. We believe it is apparent that, in the sole TPSAC meeting related to a pending application conducted to date,[2] the Committee struggled to understand the correct standard for review, which resulted in it ultimately rewording the questions posed by FDA. This unprecedented action had the effect of requiring an affirmative demonstration by the applicant that the modified risk

---

1 Tobacco Products Scientific Advisory Committee; Notice of Meeting, 82 Fed. Reg. 11226 (Feb. 21, 2017).

2 Modified Risk Tobacco Product Applications for 10 Products Submitted by Swedish Match North America Inc., FDA Docket No. FDA-2014-N-1051, available at https://www.regulations.gov/docket?D=FDA-2014-N-1051 (last accessed 03/23/17).

tobacco products ("MRTPs") at issue did not cause the disease endpoints under discussion, an impossible burden to meet.

- FDA should ensure that TPSAC members are adequately prepared for advisory committee meetings. To facilitate preparation by the Committee, briefing materials, as well as the specific questions to be addressed, should be provided well in advance of the meeting. Unfortunately, in the only example of a TPSAC meeting concerning a pending application, several TPSAC participants suggested that there was not enough time to review the materials, which hampered their ability to engage in a substantive and meaningful discussion.

- FDA should establish criteria for when it will exercise discretion and refer PMTAs to TPSAC. These criteria should include, among other things: (a) a presumption against exercising Agency discretion and referring PMTAs to TPSAC; and (b) a requirement that the Agency—if it chooses to exercise its discretion to refer a PMTA to TPSAC—explain the objective and potential benefits of obtaining TPSAC review, as well as the associated costs, in connection with a particular application. FDCA Section 917(c) outlines very specific circumstances under which TPSAC review and recommendations are to be provided to CTP. In contrast to the product-specific nature of PMTA review, these circumstances are limited to broader scientific issues applicable to multiple tobacco products. The vast majority of individual product's PMTAs will not implicate these criteria and, as a result, FDA should exercise discretion and refrain from referring PMTAs to TSPAC that do not raise these issues. In addition, as a practical matter, the pace of FDA's premarket review since passage of the TCA dictates that the Agency should avoid utilizing this additional step, which is likely to further delay final premarket review decisions, especially in view of the statutory requirement that FDA reach a decision on PMTAs within 180 days. Finally, the Agency should establish a safe harbor clarifying that newly deemed products will not be subject to enforcement if a final decision on a such a product is delayed in whole or in part on account of TPSAC review.

- FDA should not impose additional burdens on manufacturers by requiring public disclosure of the underlying PMTAs merely because the Agency subjected that particular PMTA to TPSAC review. Ample information is provided in the FDA Decision Summaries accompanying final decisions. Further, FDA is capable of developing briefing materials that do not include all the data from the underlying PMTA. Indeed, in the context of advisory committee review of new drug applications ("NDAs"), the FDA routinely develops briefing packages that do not include certain confidential data contained in NDA submissions. Manufacturers should not lose the protection of confidential information on the basis of the Agency's desire to obtain the Committee's expertise and feedback.

- The FDCA, as amended by the TCA, does not grant FDA authority to refer SE reports to TPSAC. In the Federal Register notice announcing the April 6, 2017 TPSAC meeting, the FDA included an ambiguous reference to presentation of information on the process

used to review SE reports.[3] To prevent confusion, SMARTT recommends that FDA expressly clarify that the Agency lacks statutory authority to refer SE reports to TPSAC.

BACKGROUND

The FDCA, as amended by the Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act" or "TCA"), authorized FDA to regulate the manufacture, marketing, and distribution of tobacco products in order to protect the public health and reduce tobacco use by minors.[4] Section 910 of the Tobacco Control Act requires that, unless exempted under statute, all "new tobacco products" be submitted to FDA for premarket review and approval prior to commercialization in the United States.[5] The FDCA, as amended, outlines three distinct premarket review pathways for tobacco products, including submission of a PMTA under FDCA Section 910,[6] a Substantial Equivalence ("SE") report under FDCA Section 905(j),[7] or in lieu of the latter, a request for exemption from substantial equivalence requirements under FDCA Section 905(j)(3) ("SE Exemption Requests").[8]

With respect to PMTAs, Section 910 of the FDCA provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be "appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, taking into account — (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products."[9]

In addition, the FDCA provides for premarket review of modified risk tobacco product applications ("MRTPAs"), which by statute must be referred to TPSAC for review (notably, PMTAs are not subject to mandatory TPSAC referral).[10] FDA must issue an MRTP order before an MRTP can be introduced into interstate commerce. Section 911(g)(1) of the FDCA requires FDA to issue an MRTP order based on a demonstration that a product, as actually used by consumers, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products."[11] The Tobacco Control Act outlines several factors that FDA must take into

---

3 82 Fed. Reg. 11226 (Feb. 21, 2017).

4 *See* Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 3(2), 123 Stat. 1776, 1784 (2009) (hereafter "Tobacco Control Act").

5 FDCA § 910(a); 21 U.S.C. § 387j(a).

6 FDCA § 910(b); 21 U.S.C. § 387j(b).

7 FDCA § 905(j); 21 U.S.C. § 387e(j).

8 FDCA § 905(j)(3); 21 U.S.C. § 387e(j)(3).

9 FDCA § 910(c)(4); 21 U.S.C. § 387j(c)(4).

10 FDCA § 911(f); 21 U.S.C. § 387k(f).

11 FDCA § 911(g)(1); 21 U.S.C. § 387k(g)(1).

consideration when making this determination.[12] Further, the statute requires FDA to make these determinations based on "(A) the scientific evidence submitted by the applicant; and (B) scientific evidence and other information that is made available to the [FDA]."[13]

COMMENTS

I. FDA MUST WORK TO ADDRESS SERIOUS FLAWS IDENTIFIED IN THE SOLE TPSAC PROCEEDING RELATED TO A PENDING APPLICATION

A. *FDA must ensure that TPSAC members accept the review standards provided by FDA and respond to the questions asked, as opposed to creating entirely new questions and scientific inquiries.*

Section 911(f)(1) of the FDCA provides that FDA "shall refer" to TPSAC any MRTPA submitted for review.[14] To date, TPSAC has held only one proceeding related to a pending application, which concerned the MRTPAs submitted by Swedish Match North America, Inc. ("SMNA") for its General brand snus products.[15] Unfortunately, several flaws plagued the proceeding, which, in our view, undermined the legitimacy of the Committee's conclusions. For one thing, the FDA failed to provide any guidance, either for manufacturers or TPSAC members, concerning the role of individual TPSAC members or the Committee. As a result, TPSAC members did not have a clear and consistent understanding regarding the scope of their mandate, which resulted in an erratic discussion based on the subjective views and interpretations of each individual member. Ultimately, the outcome of the meeting was ambiguous and inconsistent with FDA standards applied in other areas of FDA jurisdiction.

In particular, FDA must ensure that TPSAC members accept the review standards provided by FDA and respond to the questions asked, as opposed to creating entirely new questions and scientific inquiries. To illustrate, the questions that FDA originally posed in its briefing materials concerning the SMNA MRTPAs sought TPSAC's opinion on the adequacy of the evidence in the MRTP to demonstrate that snus posed a risk of oral cancer and dental disease — in other words, whether the evidence supported a causal relationship between snus and the identified adverse effects. Unfortunately, FDA did not clearly articulate, and TPSAC struggled to understand, the appropriate regulatory standard to apply to the evaluation of the scientific evidence supporting removal of the oral cancer and dental effects warnings. The Committee's confusion culminated in its unprecedented decision, prior to agreeing to take a vote, to reword the questions that FDA had posed for its consideration.[16] Rewording the questions posed to the

---

12 FDCA § 911(g)(4); 21 U.S.C. § 387k(g)(4).

13 FDCA § 911(g)(3); 21 U.S.C. § 387k(g)(3).

14 21 U.S.C. § 387k(f)(1).

15 U.S. Food & Drug Admin., April 9-10, 2015 – Tobacco Products Scientific Advisory Committee Meeting Announcement, available at https://www.fda.gov/AdvisoryCommittees/Calendar/ucm440606.htm (last accessed 03/23/17).

16 For example, FDA requested TPSAC's response to the following questions: "Does the evidence support that these snus products pose risks of gum disease/tooth loss/oral cancer to individual users of these

Committee had the effect of requiring an affirmative demonstration by the applicant that the MRTP products *do not* cause the disease endpoints at issue, instead of undertaking a critical evaluation of whether the weight of the evidence supports the conclusion that SMNA's products do cause those effects.

It is well established that individuals can be influenced by how information is presented or framed.[17] By requiring a demonstration of the absence of causation, rather than a demonstration of causation, TPSAC imposed a burden of persuasion that exceeds the burden applied to any other warning label regime administered by the Agency. This dichotomy is particularly striking when compared to the quantum and quality of evidence FDA requires before it will mandate that new drug applicants disclose certain information in prescription drug package inserts. For example, FDA has promulgated regulations clarifying that only "known hazards and not theoretical possibilities" can be the basis for a contraindication.[18] Similarly, to include an adverse event in the warnings and precautions section of a prescription drug's package insert, FDA regulations require "reasonable evidence of causal association" between the drug and the adverse event, although "a causal relationship need not [be] . . . definitively established."[19] In like manner, "only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event" are appropriately included in the adverse reactions section of the package insert.[20] Significantly, all of these standards require a weight of the evidence evaluation of causation, none require an applicant to prove that a causal relationship *does not* exist between the product and a potential risk.

Despite established Agency practice requiring an evaluation of causation, TPSAC abandoned this approach. Importantly, Dr. Novotny – a voting TPSAC member – identified this issue. Specifically, he pointed out that the Committee was not asked "to assert causality according to the criteria, . . . the Bradford Hill criteria; that has been used by the Surgeon General on[]. . .the relationship between risk factors and disease outcomes[,]" but rather was asked "to say that there is, you know, no risk from these activities."[21] This, of course, was precisely the question that FDA did not ask TPSAC to consider – rather, it was the question that TPSAC chose to answer.

At bottom, TPSAC improperly framed its inquiry and erroneously applied an incorrect standard when evaluating the scientific evidence presented at the April 9-10, 2015 meeting. This incorrect standard skewed the proceedings and cast serious doubts regarding the validity of

---

products?" TPSAC reworded the question as follows: "Does the evidence support that these snus products *do not* pose risks of gum disease/tooth loss/oral cancer to individual users of these products?"

17 Chris Jolls, Cass Sunstein, and Richard Thaler, *A Behavioral Approach to Law and Economics*, 50 Stan. L. Rev. 1471, 1536 (1997-1998) (describing the effects of information framing on behavior).

18 21 C.F.R. § 201.57(c)(5).

19 21 C.F.R. § 201.57(c)(6).

20 21 C.F.R § 201.57(c)(7).

21 U.S. Food & Drug Admin., Tobacco Products Scientific Advisory Committee, April 10, 2015 Meeting Transcript, at 355, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM445752.pdf (last accessed 03/23/17).

TPSAC's conclusions. In connection with future meetings, it is essential that FDA provide guidance to TPSAC members concerning the scope of their review and the proper standards to apply in Committee proceedings.

Further, applying these lessons learned from the first TPSAC meeting, the FDA must also ensure that TPSAC members are adequately prepared for advisory committee meetings. To facilitate members preparation, briefing materials, as well as the specific questions to be addressed, should be provided well in advance of the meeting. Unfortunately, in the only example of a TPSAC meeting concerning a pending application, several TPSAC participants suggested that there was not enough time to review the materials.[22] Indeed, at least one participant wondered aloud whether "a day is enough time to actually do this."[23] In the future, FDA must ensure that TPSAC is provided copies of the briefing materials and questions for consideration well in-advance of the actual meeting.

B. *FDA's presentation at the upcoming TPSAC meeting should focus on ensuring that the Committee understands and applies proper standards for review, which should be based on a weight of evidence approach.*

Requiring an applicant to demonstrate a complete absence of causation or risk, as TPSAC required in its April 9-10, 2015 hearing, exceeds the capabilities of epidemiological science. While such data may show a correlation between an agent and an effect such that causation may be implied, it cannot definitively demonstrate that a particular agent cannot, under any circumstances, cause an identified effect. Courts recognize this reality when evaluating scientific evidence for purposes of determining relevance and consistently find that expert evidence suggesting the mere possibility that a fact of consequence is true is not sufficient to have probative value.[24]

To address this limitation, FDA has historically applied a weight-of-evidence approach to Advisory Committee scientific evaluations. As recently as 2009, FDA's then-chief scientist acknowledged that "regulatory and public health decisions promulgated by the FDA are based upon the weight of scientific evidence."[25] The Center for Veterinary Medicine's (CVMs) briefing document for a Veterinary Medicine Advisory Committee meeting regarding

---

22 *See e.g.*, U.S. Food & Drug Admin., Tobacco Products Scientific Advisory Committee, April 10, 2015 Meeting Transcript, at 348-49, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM445752.pdf (last accessed 03/23/17) (Dr. Swauger stating, "I'm sort of -- I'm sitting here overwhelmed, just looking at -- just the dataset tied to this particular topic. And I'm wondering, at the end of the day, is it true, does this committee actually think that it's had enough time to digest all this material to actually make an informed recommendation?"); *Id.* at 345 (Dr. Boffetta stating, "Well, I was not very familiar with this literature, so I went back and reviewed some of the original studies, you know, last night . . .").

23 *Id.* at 349.

24 2-401 Weinstein's Federal Evidence § 401.06; *See also United States v. Ferreira*, 821 F.2d 1, 5 (1st Cir. 1987) (judge properly instructed jury to disregard evidence of mere possibility).

25 Frank M. Torti, U.S. Food & Drug Admin., *Report on Status of Regulatory Science at FDA: Progress, Plans and Challenges* (2009), available at http://www.fda.gov/ohrms/dockets/ac/09/briefing/chiefscientistrpt.html. (last accessed 03/23/17).

AquAdvantage Salmon characterizes this weight of evidence approach. CVM's guidance states that FDA generally "draw[s] on data from a number of sources including controlled studies on target populations, non-controlled studies on target populations, historical records and data, and other studies in the available scientific literature that either involve the specific product and target population or are related to the product under consideration."[26] Under the weight-of-evidence approach—as outlined by CVM—"[e]ach source, in turn, is given appropriate deference with respect to its relevance to the risk or hazard identification question under consideration."[27] Finally,"[i]rrespective of the source or order of deference given to a given dataset, all of the data and information is evaluated in the context of basic scientific principles and external validity."[28]

Generally, a weight of evidence approach to data analysis allows the decision-maker to look at all data and information, whatever its value, and give each its proper consideration[29] Unfortunately, in the sole hearing based on a pending application, TPSAC based its conclusions, not on the weight of the evidence, but on specific perceived limitations or flaws in individual studies. The Committee relied on one or a few older, limited or equivocal studies to conclude that causation or risk could not be ruled out. In the face of any scientific uncertainty, TPSAC reflexively defaulted to the current warnings without a considered evaluation of whether those warnings, in and of themselves, are scientifically appropriate as applied to the Swedish snus products in question. This approach undermined the traditional weight-of-evidence evaluation and the scientific validity of TPSAC's conclusions. Simply put, by requiring proof of the absence of causation, TPSAC gave the greatest weight to the least probative studies at the expense of a reasoned assessment of the entire body of evidence which does not now (nor did it ever) provide adequate evidence justifying the statutory warnings to Swedish snus. FDA should ensure that the TPSAC understands that a weight-of-evidence evaluation is the proper regulatory standard for any scientific evaluation conducted under the FDCA.

II. FDA MUST UTILIZE TPSAC CONSISTENT WITH THE AGENCY'S STATUTORY AUTHORITY AND IN A MEANINGFUL WAY THAT DOES NOT IMPEDE OR DELAY PENDING PREMARKET REVIEW APPLICATIONS

A. *FDA should establish criteria for when it will exercise discretion to refer a PMTA to TPSAC, including a presumption against referring a PMTA to TPSAC and an obligation to clearly delineate any benefits it believes TPSAC will provide to a specific PMTA review.*

---

[26] U.S. Food & Drug Admin., Center for Veterinary Medicine, Briefing Packet for the Veterinary Medicine Advisory Committee: AquAdvantage Salmon, 2 (Sept. 20, 2010), available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM224762.pdf. (last accessed 03/23/17).

[27] *Id.*

[28] *Id.*

[29] Joseph W. Cormier, *Advancing FDA's Regulatory Science Through Weight of Evidence Evaluations*, 28 J. CONTEMP. HEALTH L. & POL'Y 1, 11-12 (2011).

In view of the anticipated deluge of PMTAs that will be submitted in advance of the August 8, 2018 compliance period deadline outlined in the FDA's Deeming Rule[30], SMARTT believes that FDA should establish criteria for referring PMTAs to TPSAC. These criteria should include, among other things: (a) a presumption against exercising Agency discretion and referring PMTAs to TPSAC; and (b) a requirement that the Agency—if it chooses to exercise its discretion to refer a PMTA to TPSAC—explain the objective and potential benefits of obtaining TPSAC review, as well as the associated costs, in connection with a particular application. Moreover, these guidelines should clarify that the Agency does not intend to refer all PMTAs to TPSAC, but rather specify that the FDA intends to reserve TPSAC review for special situations in which the TPSAC's expertise is essential in reaching a determination on a particular application. The Agency should also highlight the specific expertise it believes TPSAC would offer in reviewing a particular application, so that only these relevant areas of expertise become the focus of TPSAC review.

FDCA Section 917(c) states that the TPSAC "shall provide advice, information, and recommendations" to FDA if such review is mandated by statute or concerning the following topics: (i) on the effects of the alteration of the nicotine yields from tobacco products; (ii) on whether there is a threshold level below which nicotine yields do not produce dependence on the tobacco product involved; and (iii) on TPSAC's review of other safety, dependence, or health issues relating to tobacco products as requested by FDA.[31] These topics are confined to broader scientific questions applicable to multiple tobacco products, as opposed to the narrow product-specific inquiry embodied by PTMA review. Because the overwhelming majority of PMTAs will not raise the issues discussed in Section 917(c), the FDA should exercise discretion and refrain from referring PMTAs to TPSAC for review.

As a practical matter, the pace of FDA's premarket review since passage of the TCA dictates that the Agency should avoid creating additional steps which are likely to further delay final premarket review decisions. All the more because the FDCA includes a statutory requirement that FDA reach a decision on PMTAs within 180 days.[32] Indeed, FDA has struggled to keep up with the Agency's premarket review workload and has consistently failed to meet its own performance measures. The FDA has received a total of 6,589 Product Applications—premarket applications, regular and provisional SE Reports, exemptions, and modified risk submissions—since program inception, and only 2,819 have received Final Actions, representing a 42.8% completion rate.[33] Once PMTA refuse-to-accept and refuse-to-file

---

30 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, 81 Fed. Reg. 28974, 28978 (May 10, 2016) [hereafter "Deeming Rule"].

31 FDCA § 910(c); 21 U.S.C. § 387q(c).

32 FDCA § 910(c)(1)(A); 21 U.S.C. § 387j(c)(1)(A).

33 U.S. Food & Drug Admin., *Cumulative Number of Product Applications Received Since Program Inception*, available at http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=ctp&id=%20CTP-OS-total-product-submissions-since-Program-Inception (last updated Sept. 30, 2016) (last accessed 03/23/17).

decisions[34], regular and streamlined SE Report withdrawals[35], and Same Characteristic SE Report cancellations[36] are removed from the total number of "final actions", the Agency's completion rate falls to 6.4%. Simply put, FDA has issued final orders granting or denying a PMTA or SE Report for *fewer than 7%* of total submissions received, despite the fact that over six years have elapsed since industry submitted more than 3,500 Provisional SE Reports before the March 22, 2011 statutory grace deadline. Even if one classifies PMTA and SE Report "refuse-to-accept" and "refuse-to-file" decisions as "final actions," eliminating only SE Report withdrawals and cancellations from the total number of "final actions," there is still only a 16.5% completion rate. Moreover, the preliminary evidence suggests that TPSAC review further postpones already delayed final actions. Indeed, FDA failed to achieve its performance goals with respect to SMNA's MRTPAs (*i.e.*, the only MRTPAs that have been subject to TPSAC review). Over twenty months elapsed between the TPSAC hearing and the FDA's final action on SMNA's MRTPAs, a review timeframe well-past FDA's 360 day performance goal.[37]

Given the sheer volume of submissions received by the FDA to date, it comes as no surprise that the Agency has spent much of its limited resources attempting to manage the premarket process. In fact, even though the FDCA does not permit the Agency to ban tobacco products, FDA's current approach to premarket review (and SE review, in particular) freezes the status quo and acts as a *de facto* ban on new products, including any innovative or improved products.[38] SMARTT attributes these dramatic and systemic flaws in the current premarket review process to two distinct issues, namely: (i) an underestimation by the FDA of the annual number of premarket review filings to be submitted to the Agency; (ii) a rigid interpretation of the grandfather and substantial equivalence provisions of the Act.[39]

Most notably for purposes of this docket, the FDA grossly underestimated the total number of premarket review filings that the Agency would receive each year for currently regulated products. In January 2011, the Agency estimated that 150 firms would each submit 1

---

34 U.S. Food & Drug Admin., Tobacco Product Marketing Orders, available at https://www.fda.gov/tobaccoproducts/labeling/marketingandadvertising/ucm339928.htm (last accessed 03/23/17) (identifying 362 PMTA Final Actions as "Refuse-to-Accept" and 4 as "Refuse-to-File").

35 *Id.* (identifying 1,328 regular and streamlined SE report withdrawals as of Jan. 17, 2017).

36 *Id.* (identifying 405 Same Characteristic SE Report Cancellations as of Jan. 17, 2017).

37 U.S. Food & Drug Admin., *Current CTP performance measures for cigarettes, cigarette tobacco, smokeless tobacco, and roll-your-own tobacco*, available at https://www.fda.gov/tobaccoproducts/labeling/tobaccoproductreviewevaluation/substantialequivalence/ucm475489.htm (last accessed 03/23/17).

38 SMARTT believes that this *de facto* ban is a clear violation of the Act, as Congress has explicitly prohibited FDA from banning "all cigarettes, all smokeless tobacco products, all little cigars, all cigars other than little cigars, all pipe tobacco, or all roll-your-own tobacco products" or "requiring the reduction of nicotine yields of a tobacco product to zero." FDCA § 907(d)(3); 21 U.S.C. § 387g(d)(3).

39 SMARTT submitted multiple comments when FDA first implemented the SE review process that identified these flaws and correctly predicted the outcome that FDA is struggling with today. *See e.g.*, Commonwealth Brands, JT International U.S.A., King Maker Marketing, Nat Sherman, and Swedish Match Comment, FDA-2010-D-0635-0009 (noting that "a broad interpretation of the Section 905(j) reporting mandate – as manifested in the SE Guidance – will impose an incredible and unnecessary administrative burden on the Agency and the tobacco product manufacturing industry.").

SE Report or PMTA per year, such that the FDA would review only 150 premarket submissions in a given year.[40] However, firms have submitted more than 6,492 SE Reports and PMTAs since the March 2011 deadline for Provisional SE Reports.[41] This averages to 1,082 submissions annually over the last six years, or *more than seven times* FDA's initial estimate. In hindsight, it is clear that the Agency was ill-equipped to handle such a heavy volume of submissions, particularly where several thousands of submissions spanning multiple product classes came flooding in to the FDA at the same time.

And the FDA does not appear to have learned from its mistakes. In the Deeming Rule, the FDA estimated that it would receive "335 Full SE Initial reports," "250 Full SE Bundled Reports," "418 Same Characteristics SE Reports," "139 Initial Product Quantity Change reports," and "55 Product Quantity Change Bundled SE Reports" amounting to a total of 1,197 SE reports annually.[42] In addition, the Agency estimated that it would receive 750 PMTAs on an annual basis.[43] Although SMARTT believes these estimates significantly underestimate the likely number of actual submissions, especially with respect to ENDS products, the larger issue is that the FDA has demonstrated that it lacks the resources and administrative capacity to handle the anticipated volume of submissions. Nevertheless, the FDA has refused to implement a flexible regulatory approach aimed at addressing the issues created by the slow pace of the Agency's review. Rote referral of PMTAs to TPSAC will only serve to increase the burden and delay.

In view of the limitations on the FDA's review capacity imposed by resource constraints, SMARTT proposes that, at a minimum, FDA establish a safe harbor, which clarifies that newly deemed products will be considered to have "made substantial progress toward completion,"[44]—and therefore not be subject to enforcement action—if a final decision on such a product's PMTA is delayed, in whole or in part, because of TPSAC review. This safe harbor would encourage FDA to evaluate whether TPSAC review is necessary for a PMTA while simultaneously ensuring that individual tobacco manufacturers are not unfairly targeted for enforcement on account of the Agency's desire to consult the Committee.

---

40 Agency Information Collection Activities; Proposed Collection; Comment Request; Guidance for Industry and Food and Drug Administration Staff; Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products, 76 Fed. Reg. 4116 (Jan. 24, 2011).

41 6,492 total applications excludes the 97 SE Exemption requests received since program inception. *See* U.S. Food & Drug Admin., *Cumulative Number of Exemption from SE Applications received since Program Inception*, available at http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=ctp&id=%20CTP-OS-total-exemption-from-SE-since-Program-Inception available at (last updated Sept. 30, 2016) (last accessed 03/23/17).

42 Deeming Rule, 81 Fed. Reg. 28974, 29088 (May 10, 2016).

43 *Id.* at 29091.

44 *Id.* at 28978 (". . . if at the time of the conclusion of the continued compliance period, the 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.").

Regardless, the FDA should provide a detailed justification that explains the benefits that TPSAC's review will provide to the Agency's implementation of the PMTA review process, especially given the tight review deadline created by the twelve month continued compliance period established by the Deeming Rule.[45] In particular, the FDA ought to establish clear guidance explaining, in concrete terms, the benefits FDA hopes to obtain from TPSAC review of PMTAs. The TPSAC has neither the time nor resources to devote to thoroughly studying thousands of individual product applications. Indeed, SMARTT observes that TPSAC members are likely to be unfamiliar with the fine points of CTP's review process, historical precedent, or the applicable review standards (as demonstrated in the first TPSAC hearing). As such, the TPSAC will require extensive education from CTP staff for each meeting. In turn, these education efforts divert Agency resources from the ever-growing review queue as resources are redirected toward the TPSAC. Moreover, if PMTAs are routinely referred to TPSAC, such reviews will impose extensive costs on tobacco product manufacturers as a consequence of the vast resource outlay required to prepare for even an unsuccessful meeting. Accordingly, FDA ought to clearly elaborate the concrete benefits the Agency hopes to receive from TPSAC review, which purport to justify imposition of the associated resource drain on CTP and substantial costs on manufacturers.

FDA's current approach to premarket review is further complicated by the Agency's interpretation of the grandfather provisions of the Tobacco Control Act. As set forth in the preamble to the Deeming Rule, "FDA has determined that it lacks authority to change the grandfather date, which is set by statute"[46] notwithstanding the fact that the Agency was only able to identify a single ENDS product, "a non-flavored e-cigarette,"[47] that was on the market prior to February 15, 2007. By consequence, the FDA's interpretation effectively subjects the entire class of electronic nicotine delivery systems (ENDS) to the PMTA premarket review process.[48] Notably, FDA expressly recognized in the Deeming Rule that "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."[49] Imposition of TPSAC review on a class-wide basis is likely to impose significant delays and impede market access for manufacturers of an entire category of products that FDA acknowledges present "less risk."

With these considerations in mind, SMARTT urges FDA to establish criteria for referring PMTAs to TPSAC, including: (a) a presumption against exercising Agency discretion and referring PMTAs to TPSAC; and (b) a requirement that the Agency—if it chooses to exercise its discretion to refer a PMTA to TPSAC—identify the objective and potential benefits of obtaining TPSAC review, as well as the associated costs, in connection with a particular application.

---

45 *Id.* at 28978 ("For newly deemed tobacco products using the PMTA pathway, this continued compliance period will close 36 months after the effective date (i.e., 12 months after the 24-month compliance period closes for submission and receipt of PMTAs).").

46 Deeming Rule, 81 Fed. Reg. 28974, 28993 (May 10, 2016).

47 *Id.* at 28991.

48 *Id.* at 28993.

49 *Id.* at 28981.

B. *FDA should clarify whether any of the TPSAC review process covering PMTAs will be publicly accessible.*

The FDCA, as amended by the TCA, requires FDA to make MRTPAs available to the public (except for matters that are trade secrets or otherwise confidential commercial information) and to request comments by interested persons on the information contained in the application and on the label, labeling, and advertising accompanying the application.[50] By contrast, Section 910 of the FDCA is silent with respect to whether PMTAs must be made available to the public. SMARTT opposes making PMTAs publicly available as such action would likely result in disparate treatment of select PMTAs should they be subject to TPSAC review.

As discussed above, SMARTT believes that the FDA should establish a presumption against TPSAC review of PMTAs. Under this proposal, the vast majority of PMTAs would not be subject to TPSAC review because such review would be limited to special situations requiring the Committee's expertise. Given that full PMTAs—as opposed to FDA Decision Summaries—are not publicly available in the conventional review process, FDA should not increase the burden on the group of manufacturers whose PMTAs may be the subject of TPSAC review. Simply put, the FDA should not impose an additional public disclosure burden on manufacturers on the basis of the Agency's desire to obtain the Committee's expertise and feedback.

In the context of advisory committee review of NDAs, the FDA routinely develops briefing materials that summarizes and/or omits certain confidential data included in the underlying application. The FDA should employ a similar approach to TPSAC briefing materials. All the more because of the great potential for the public to misinterpret certain information, such as HPHC data, in the absence of the appropriate context and analysis. At any rate, the public will have access to certain aspects of the application when the FDA issues its Decision Summary on the PMTA in question. With that in mind, SMARTT believes that public access to full PMTAs would improperly burden select manufacturers while simultaneously providing unhelpful and potentially misleading information.

C. *FDA should expressly confirm that the Agency lacks statutory authority to refer SE reports to TPSAC.*

In the Federal Register notice announcing the April 6, 2017 TSPAC meeting, the FDA included an ambiguous reference to presentation of information on the process used to review SE reports.[51] SMARTT believes that the FDA should expressly clarify that the Agency lacks statutory authority to refer SE reports to TPSAC. As the FDA is aware, the FDCA, as amended by the Tobacco Control Act, applies a different regulatory framework to TPSAC review of MRTPAs and PMTAs. In particular, Section 911(f) of the FDCA expressly states that FDA "shall refer" to the TPSAC any MRTPA submitted under that section, but grants FDA discretion concerning referral of PMTAs to the Committee.[52] Importantly, Congress failed to grant FDA

---

50 FDCA § 911(e); 21 U.S.C. § 387k(e).

51 82 Fed. Reg. 11226 (Feb. 21, 2017).

52 *Compare* FDCA § 911(f)(1) (21 U.S.C. § 387k(f)(1)); FDCA § 910(b)(2) (21 U.S.C. § 387j(b)(2)).

authority to refer SE reports to TPSAC, despite expressly referencing such referral authority in the context of PMTAs and other provisions of the Tobacco Control Act.[53] To illustrate, with respect to PMTAs, the statute provides that "[u]pon receipt of an application meeting the requirements set forth in [FDCA 911(b)(1)]," FDA may on its own initiative or at the request of an applicant, refer an application to TPSAC.[54] As such, the statutory prerequisite for TPSAC referral is receipt of an application that meets the requirements of FDCA Section 910(b)(1). By its nature as an abbreviated application, an SE report will never meet these stringent requirements. As a result, Section 910(b)(2) does not provide statutory authority to refer SE reports to TPSAC.

This reading is confirmed by examining Section 905(j) of the FDCA, which addresses the requirements for submission of SE Reports.[55] Notably, this section does not include an analogous TPSAC referral provision akin to those included in the statutory sections discussing the MRTPA and PMTA requirements. By consequence, the best reading of the Act is that it does not grant FDA statutory authority to refer SE reports to TPSAC. Moreover, this result is compelled by practical considerations. As FDA is well-aware, there are literally thousands of SE reports currently sitting in CTP's review queue. Adding another step in the premarket review process would further delay final decisions and undermine implementation of the statutory scheme.

* * * *

We thank you in advance for your consideration of our recommendations, and appreciate this opportunity to share our perspectives with the Agency. We look forward to continuing to assist the FDA in its efforts to protect the public health through reasonable regulation devoid of unnecessary burdens on either the Agency or regulated industry.

Respectfully,

Paisley Cameron
Scientific & Regulatory Affairs Director, Americas
JT International U.S.A., Inc.

Rhondetta Walton
Vice President, Regulatory Compliance
Commonwealth Brands, Inc.

---

53 *See e.g.*, FDCA § 906(e)(1)(B),(e)(2)(B), 907(d)(5),(e)(1),(f)(1); 21 U.S.C. § 387f(e)(1)(B), (e)(2)(B), 21 U.S.C. § 387g(d)(5),(e)(1),(f)(1).

54 FDCA § 910(b)(2)(A)-(B); 21 U.S.C. § 387j(b)(2)(A)-(B).

55 FDCA § 905(j); 21 U.S.C. § 387e(j).