FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File
From:	Anne Radway, M.S. Associate Director Division of Regulatory Project Management Office of Science For Rosanna Beltre -S Digitally signed by Rosanna Beltre -S Date: 2021.07.09 11:28:49 -04'00'
Through:	Matthew Holman, Ph.D. Director Office of Science Digitally signed by Matthew R. Holman -S Date: 2021.07.09 11:33:09 -04'00'
Subject:	ENDS Containing Non-Tobacco Flavored E-Liquid: Approach to PMTAs[1] not in Substantive Scientific Review (Phase III)

Background

As of September 9, 2020, FDA commenced review of premarket applications for electronic nicotine delivery systems (ENDS) products on the market as of August 8, 2016; applicants were required by a court order to submit applications to FDA by this date. The majority of these applications are for non-tobacco flavored ENDS products.[2] To date, OS has implemented its plan to review a subset of these applications in this first year: the PMTAs selected for review were identified using a plan described in the Premarket Application Review Prioritization Plan memorandum[3], signed August 31, 2020. Office of Science has been tasked with developing a new plan to effectively manage the remaining non-tobacco flavored ENDS PMTAs not in Phase III, substantive scientific review. This task has been assigned by the Acting Commissioner given the likely impact on the marketplace on September 10, 2021 (the end of the enforcement discretion period for deemed tobacco products) and in order to take final action on as many applications as possible by September 10, 2021. The objective is to address these applications by applying a standard for evidence necessary to demonstrate an incremental benefit to adult smokers of non-tobacco flavored ENDS products.

Discussion

As described in Section 910 of the FD&C Act, to receive marketing authorization under the PMTA pathway, FDA must conclude that the marketing of the product is appropriate for the protection of public health (APPH), including both tobacco users and nonusers. Based on the information available to date, FDA has determined this evaluation requires evidence that can demonstrate whether an applicant's new non-tobacco flavored product(s) will provide an incremental benefit to adult smokers relative to the applicant's tobacco-flavored product(s). In particular, the evidence necessary for this evaluation would be provided by either a randomized controlled trial (RCT) or a longitudinal cohort

[1] Premarket Tobacco Product Applications
[2] Refers to open e-liquids, closed e-liquids, and closed e-cigarettes containing non-tobacco flavored e-liquid
[3] See addendums dated September 24, 2020 and May 11, 2021

study. The absence of these types of studies is considered a fatal flaw, meaning any application lacking this evidence will likely receive a marketing denial order (MDO).

Considering the large number of applications that remain to be reviewed by the September 9, 2021 deadline, OS will conduct a Fatal Flaw review of PMTAs not in Phase III for non-tobacco flavored ENDS products. The Fatal Flaw review is a simple review in which the reviewer examines the submission to identify whether or not it contains the necessary type of studies. The Fatal Flaw review will be limited to determining presence or absence of such studies; it will not evaluate the merits of the studies. To decrease the number of PMTAs without final action by September 9, 2021, OS used a database query to identify the top twelve[4] manufacturers with the largest number of pending PMTAs not in Phase III[5] for non-tobacco flavored e-liquid products. These applications were pulled out of their respective place in the PMTA priority list, and Phase II Filing was initiated (see Appendix A). Following completion of filing those applications that are filed will immediately initiate Fatal Flaw review.

For the remaining PMTAs not in Phase III for non-tobacco flavored e-liquid products, FDA will send an General Correspondence letter requesting the applicant to confirm if their PMTA contains such evidence and, if so, to direct FDA to the location in the application where the studies can be found. Manufacturers eligible for this process, OS is identifying open PMTAs submitted from April 1, 2020 to September 9, 2020 that have been Received, Accepted and/or Filed and have not entered Phase III. Additionally, PMTAs were filtered based on product characterizing flavor (non-tobacco flavors), product type (i.e., open or closed e-liquid or closed e-cigarette), and category/subcategory (i.e., Other/Other). General Correspondence letters will be issued to companies listed in Appendix B. If later FDA discovers a manufacturer was not issued a General Correspondence letter when they should have been, the applications will be evaluated on a case-by-case basis.

[4] These applications represent 85% of all pending PMTA applications.

[5] These will be the same manufacturers/PMTAs as identified for prioritized Filing Reviews in the June 30, 2021, memorandum.

Appendix A

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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File	
From:	Benjamin Apelberg, PhD Deputy Director Office of Science	Digitally signed by Benjamin Apelberg -S Date: 2021.08.17 14:04:15 -04'00'
Through:	Matthew R. Holman, PhD Director Office of Science	Digitally signed by Matthew R. Holman -S Date: 2021.08.17 16:06:36 -04'00'
Subject:	PMTA[i] Review: Evidence to Demonstrate Benefit of Flavored[ii] ENDS[iii] to Adult Smokers	

Purpose

The purpose of this memo is to describe our findings with respect to the type of evidence that may support a finding that the marketing of a flavored ENDS[iv] is appropriate for the protection of the public health (APPH), in light of the significant concerns that flavored ENDS present with respect to youth appeal, uptake, and use.[v] Specifically, FDA has determined that the known and substantial risk to youth posed by flavored ENDS establishes a high burden for applicants seeking to demonstrate a potential benefit to adult smokers[vi] that could justify that risk. Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined that, to effectively demonstrate this benefit in terms of product use behavior, the strongest types of evidence should be submitted—most likely product specific evidence from a (1)

[i] Premarket Tobacco Product Application

[ii] Throughout this memo, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

[iii] Electronic Nicotine Delivery System

[iv] For the purpose of this memo, we do not include menthol in the category of *flavored ENDS*. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other non-tobacco-flavored ENDS, raises unique considerations. As a result, menthol ENDS PMTAs are not included in the scope of this memorandum, although the statute similarly imposes a high burden to demonstrate a benefit to existing users given the known youth use of menthol ENDS products.

[v] This memo applies to all sub-categories of ENDS, including unflavored "base" e-liquids that are designed to have flavors added to them. This includes e-liquids made for use with open systems as well as closed system ENDS (e.g., cartridges or disposable ENDS) containing e-liquids. Devices determined to include technology to lock the device or otherwise effectively limit access to adult users of legal age are outside the scope of this memo.

[vi] The standard described in Section 910 requires an accounting of the risks and benefits to the population as a whole, balancing the potential impacts to both current tobacco users and non-users. Because the focus of this memo is on ENDS, and further, the potential benefit of ENDS to the population health, we focus our discussion of current users on adult smokers, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

randomized controlled trial (RCT)[vii] or (2) longitudinal cohort study.[viii,ix] Moreover, tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Therefore, to meet the high burden to demonstrate the potential benefit to current users, a PMTA for flavored ENDS should include a demonstration with acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.

We intend to conduct a streamlined scientific review of PMTAs for flavored ENDS to determine whether the applications contain evidence of this type. For those that do, we will refer them for further in-depth scientific evaluation as to whether the evidence satisfies that statutory standard for authorization. In the absence of this evidence, we generally intend to issue a marketing denial order. In this memo, we describe the background for this approach, document the scientific evidence related to youth risk, and describe the rationale that informs our determination of the types of evidence that should be submitted to overcome this risk and potentially support a determination that the new product's marketing would be considered APPH.

Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) requires that "new tobacco products" receive marketing authorization from FDA under one of the pathways specified by the Act in order to be legally marketed in the United States. Under one pathway, the applicant submits a premarket tobacco product application (PMTA) to FDA. Section 910 of the FD&C Act requires that, for a product to receive PMTA marketing authorization, FDA must conclude, among other things, that the marketing of the product is APPH. The statute specifies that, in assessing APPH, FDA consider the risks and benefits to the population as a whole including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products.

FDA had previously set an extended compliance deadline for the submissions of PMTAs. That extension was challenged in court, which reset the deadline.[x] Consistent with that court order, premarket applications for many new tobacco products, including ENDS currently on the market, were due to FDA

[vii] A randomized controlled trial is a clinical investigation or a clinical study in which human subject(s) are prospectively, and randomly assigned to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on behavioral, biomedical, or health-related outcomes. *Control or controlled* means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.*, historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures.

[viii] A longitudinal cohort study is an observational study in which human subjects from a defined population are examined prospectively over a period of time to assess an outcome or set of outcomes among study groups defined by a common characteristic (e.g., smoking cessation among users of flavored ENDS compared with users of tobacco-flavored ENDS).

[ix] We would also consider evidence from another study design, provided that it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products. In our review of PMTAs for flavored ENDS so far, we have learned that, in the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. Further discussion on types of evidence can be found in this memo (see "Behavioral evidence appropriate to demonstrate the potential benefit to smokers").

[x] *American Academy of Pediatrics. v. FDA*, 379 F. Supp. 3d 461 (D. Md. 2019) (vacating guidance); *American Academy of Pediatrics v. FDA*, No. 8:18-cv-883, Dkt. No. 182 (D. Md. Apr. 22, 2020) (resetting deadline).

by September 9, 2020.

The vast majority of these applications are for flavored ENDS. It is well recognized that ENDS, and particularly flavored ENDS, pose a significant risk to nonusers, especially youth.[1,2] After observing a dramatic increase in the prevalence of ENDS use among U.S. youth in 2018, FDA's Commissioner characterized the problem as a youth vaping epidemic. FDA has initiated a series of actions to address the risk and reduce youth use. Since August 2016, FDA has issued more than 10,000 warning letters and more than 1,400 civil money penalty complaints to retailers for the sale of ENDS products to minors. FDA has also issued a guidance that described a policy of prioritizing enforcement of non-tobacco/non-menthol flavored ENDS, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market without Premarket Authorization." In this guidance, FDA described evidence that shows flavors (other than tobacco and menthol) were a key driver of the surge in ENDS use among youth and thus prioritized enforcement against certain flavored ENDS products, with the goal of protecting youth from these products.[xi]

After FDA implemented this enforcement policy prioritizing enforcement against a subset of ENDS products known to appeal to youth, there was a meaningful reduction in youth use prevalence. Youth ENDS use peaked in 2019 when these products were widely available. Although several other policy changes and interventions were occurring during this same time period,[xii] it is reasonable to infer that prioritizing enforcement against many flavored products resulting in their removal from the market contributed to the decline in use in 2020. Despite this decline, ENDS remained the most widely used tobacco product among youth, with youth use at levels comparable to what originally led FDA to declare a youth vaping epidemic. Moreover, despite the overall reduction in ENDS youth use observed in 2020, there was simultaneously a substantial rise in youth use of disposable ENDS, products that were largely excluded from the enforcement priorities set forth in the enforcement policy because at that time they were the least commonly used device type among high school ENDS users and therefore remained on the market as a flavored option.[3,4]

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be [APPH]." Through the PMTA review process, FDA conducts a science-based evaluation to determine whether marketing of a new tobacco product is APPH. Section 910(c)(4) requires FDA, in making the APPH determination, to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco, and take into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (See Section 910(c)(2)). As described in greater detail below, in reviewing PMTAs for flavored ENDS, FDA evaluates, among other things, the potential benefit to adult smokers who may transition away from combustible cigarettes to the ENDS product, weighed against the known risks of flavored ENDS to youth.

[xi] Due to the overwhelming amount of evidence showing a substantial increase in youth use of flavored ENDS products, as well as their demonstrated popularity among youth, in January 2020, FDA finalized a guidance prioritizing enforcement against flavored (other than tobacco or menthol) prefilled pod or cartridge-based e-cigarettes, as well as other categories of unauthorized products.

[xii] The change in ENDS product availability coincided with other events such as the enactment of legislation raising the federal minimum age for sale of tobacco products from 18 to 21 years (Tobacco 21), the outbreak of e-cigarette, or vaping, product-use associated lung injury (EVALI), and public education campaigns which also may have contributed to the decline in ENDS use.

The Risk to Youth of Flavored ENDS Products

As noted, the APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood[5] and thus youth are at particular risk of tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

Youth use of flavored ENDS

ENDS are now the most commonly used type of tobacco product among youth. In 2020, approximately 19.6% of U.S. high school students and 4.7% of middle school students were current users of ENDS, corresponding to 3.6 million youth and making ENDS the most widely used tobacco product among youth by far.[8] As noted above, this was a decline from 2019, when 27.5% of high school and 10.5% of middle school students reported ENDS use,[9] which necessitated the FDA enforcement policy described above.

FDA has concluded that the availability of a broad range of flavors is one of the primary reasons for the popularity of ENDS among youth. The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time. In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school e-cigarette[xiii] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xiv] increased to 84.7% of high school users and 73.9% of middle school users.[3] Among high school e-cigarette users, the most common flavors used in 2020 were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, dessert, or other sweets (36.4%).[3] Among middle school e-cigarette users, the most common flavors used in 2020 were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%).[3]

Youth ENDS users are also more likely to use flavored ENDS compared to adult ENDS users. In PATH Wave 5.5 from 2020, 66.8% of youth ENDS users aged 13 to 17 reported using fruit, followed by 53.8% for mint/menthol[xv], 23.5% for candy/dessert/other sweets, and 13.3% for tobacco flavor (internal analysis). In the 2020 PATH Adult Telephone Survey, 51.5% of adult ENDS users 25 and older used fruit, 30.4% used mint/menthol, 23.8% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor and to use combinations that did not include tobacco flavors.[11]

[xiii] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[xiv] Flavored product use in these studies means use of flavors other than tobacco.
[xv] The PATH Study Questionnaire from Wave 5.5 did not assess mint and menthol separately. However, subsequent data collections (ATS and Wave 6) have separated the two flavors.

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first e-cigarette that they used was flavored.[12] In another PATH study, more youth, young adults and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product.[13] Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[14]

In addition, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason.[15,16] In fact, among Wave 4 youth current ENDS users, 71% reported using ENDS "because they come in flavors I like."[14]

One explanation for this high prevalence and increase in frequency of use is that flavors can influence the rewarding and reinforcing effects of e-liquids, thereby facilitating ENDS use and increasing abuse liability. Research shows that flavored ENDS are rated as more satisfying than non-flavored ENDS, and participants will work harder for and take more puffs of flavored ENDS compared to non-flavored ENDS.[17] Research also shows that flavors can increase nicotine exposure by potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use.[18] Together, this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain, which is discussed further below.

Finally, existing literature on flavored tobacco product use suggests that flavors not only facilitate initiation, but also promote established regular ENDS use. In particular, the flavoring in tobacco products (including ENDS) make them more palatable for novice youth and young adults, which can lead to initiation, more frequent and repeated use, and eventually established regular use. For example, regional studies have found that the use of flavored e-cigarettes was associated with a greater frequency of e-cigarettes used per day among a sample of adolescents in Connecticut in 2014[19] and continuation of e-cigarette use in a sample of adolescents in California from 2014-2017.[20] Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode.[20] Data from a regional survey in Philadelphia, PA found initial use of a flavored (vs. unflavored or tobacco flavored) ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months.[21] Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where "ever use" of flavored e-cigarettes at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2.[22] In sum, flavored ENDS facilitate both experimentation and progression to regular use, which could lead to a lifetime of nicotine dependence.

The appeal of flavors across ENDS devices

The appeal of flavors applies across the entire class of ENDS on the market. Indeed, the role of flavors in increasing the appeal of tobacco products to youth — across tobacco product categories — is well-established in the literature.[23-26]

National surveillance data suggest that, within the ENDS category, there is variability in the popularity of device types among youth, suggesting there may be differential appeal of certain product styles. Still,

across these different device types, the role of flavor is consistent. As described above, the majority of youth ENDS use involves flavored products: in 2020, the majority of high school and middle school current e-cigarette users reported use of non-tobacco-flavored products (82.9%)[3] and flavored use was favored among both users of closed (87%) and open (76%) ENDS (internal analysis). In particular, across device types, including prefilled pods/cartridges, disposables, tanks, and mod systems, fruit was the most commonly used flavor type among youth, with 66.0% for prefilled pods/cartridges, 82.7% for disposables, 81.7% for tanks, and 78.9% for mod systems among youth reporting using a fruit flavor.[3]

It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace following the 2020 enforcement priorities guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based devices.[xvi] Then, as noted earlier, when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS[xvii]--a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users.[4] This trend illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor options, underscoring the fundamental role of flavor in driving appeal.

The harms of youth ENDS use: The adolescent brain and risk for addiction

In addition to the high prevalence of youth ENDS use, the data also suggest this use is leading to increases in nicotine dependence.[10] Indeed, responding to concerns related to youth ENDS dependence, at the end of 2018, FDA held a public hearing to discuss the potential role of drug therapies to support e-cigarette cessation.[xviii]

In 2019, an estimated 30.4% of middle and high school student ENDS users reported frequent use (i.e., use on ≥20 of the past 30 days).[9] By school type, 34.2% (95% CI, 31.2%-37.3%) of high school student ENDS users and 18.0% (95% CI, 15.2%-21.2%) of middle school student ENDS users reported frequent use.[27] Among current ENDS users, 21.4% of high school users and 8.8% of middle school users reported daily ENDS use.[27] Additionally, in a study that examined changes in ENDS use in youth ages 13-18 over a 12-month period, nicotine dependence (measured using the Penn State Electronic Cigarette Dependence Index (PS-ECDI)[28,29] and salivary cotinine concentrations increased, indicating continued ENDS use and greater nicotine exposure over time.[30]

Youth and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development.[31,32] Adolescence is a developmental period consisting of major neurobiological and psychosocial changes and is characterized by increased reward-seeking and risk-taking behaviors (e.g., experimentation with drugs), coupled with heightened sensitivity to both natural and drug rewards and an immature self-regulatory system that is less able to modulate reward-seeking

[xvi] This is borne out by the data from 2019 NYTS, in which 59.1% of high school ENDS users reported use of this one brand. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. Jama. 2019;322(21):2095-2103.

[xvii] In July 2020, FDA issued Warning letters to three companies for illegally marketing disposable e-cigarettes and for marketing unauthorized modified risk tobacco products.

[xviii] On December 5, 2018, FDA hosted a public hearing on "Eliminating Youth Electronic Cigarette and Other Product Use: The Role of Drug Therapies."

impulses (e.g., diminished harm avoidance, cognitive control, self-regulation).[33-37] Furthermore, evidence from animal studies suggests that nicotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood [38-41]; and can induce short and long-term deficits in attention, learning, and memory.[42-45]

Risk of progression from ENDS to other tobacco products of different health risk

Among youth who use ENDS, there is a risk of progression to other tobacco products of greater health risk. A 2017 systematic review and meta-analysis that summarized nine prospective cohort studies found significantly higher odds of smoking initiation (OR = 3.50, 95% CI: 2.38, 5.16) and past 30-day combusted cigarette use (OR = 4.28, 95% CI: 2.52, 7.27) among youth who had used ENDS at compared to youth who had not used ENDS.[46] Similar associations have been observed in longitudinal studies that have been published since the Soneji et al. review.[42,47-56] The 2018 NASEM report concluded that there is substantial evidence that ENDS use increases risk of ever using combusted tobacco cigarettes among youth and young adults.[57] The transition from non-cigarette product use to combusted cigarette use has been observed for other non-cigarette products, such as cigars, as well.[58] Although it is challenging to empirically separate causality from shared risk factors among youth combusted cigarette and ENDS users, some studies have found an association between ENDS and subsequent combusted cigarette use while controlling for similar risk profiles.[54]

The precise relationship between youth ENDS use and youth smoking remains undetermined. On the one hand, the prevalence of combusted cigarette smoking in youth has continued to decline,[9,59,60] suggesting that youth use of ENDS has not significantly slowed or impeded that positive public health trajectory. On the other hand, there is a growing body of evidence showing a link between ENDS use and subsequent smoking among youth that raises significant concerns. This evidence also increases concern that over time—and particularly if youth ENDS use were to return to the rates seen in 2019 or worsen--the trend of declining cigarette smoking could slow or even reverse.

Other health risks associated with ENDS use

In addition to the risk of tobacco initiation and progression among youth, there is epidemiologic evidence from the cross-sectional[xix] Behavioral Risk Factor Survey system (BRFSS) suggesting positive associations between ENDS use among those who never smoked and some health outcomes. Two studies found associations between ENDS use and self-reported history of asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease with increased ENDS use (i.e., daily use) relating to increased odds of disease.[61,62] Another found an association between ENDS use and respiratory symptoms in younger adults (ages 18-34) but not in older adults.[63] ENDS use has also resulted in acute harm to individuals through battery explosion-related burns and e-liquid nicotine poisoning.[64-66] Ultimately, as this is still a relatively novel product category, much remains unknown about other potential long-term health risks.

Conclusion

The exponential growth in youth ENDS use observed from 2017 to 2019, and the enduring prevalence of youth ENDS use in the U.S. is alarming. Despite a reduction in youth use of ENDS from 2019 to 2020, there were still 3.6 million youth ENDS users in 2020 and the majority used a flavored ENDS product. Youth users are more likely to use flavored ENDS than adult ENDS users. Flavors are associated with ENDS initiation and progression among youth. The full extent of the harms of ENDS use are not yet

[xix] Cross-sectional surveys examine these relationships at a single point in time, and as a result, do not establish causality.

known, but evidence to date suggests they include permanent effects of nicotine on the developing adolescent brain and the risk of nicotine addiction. Studies indicate an additive effect of e-liquid flavorings on the rewarding and reinforcing effects of nicotine containing e-liquids. Studies also demonstrate that e-liquid flavors affect nicotine exposure. Among youth who use ENDS, there is a risk of progression to other tobacco products with greater health risks including combustible cigarettes. Finally, though long-term health risks are not fully understood, studies suggest an association between never-smoking ENDS users and respiratory and cardiovascular health effects. This evidence strongly supports the finding that flavored ENDS pose a significant risk to youth. Moreover, because the appeal of flavor is consistent across ENDS device types, and the harms to youth posed by flavored ENDS use, including nicotine dependence, are not moderated by device type, we find that this conclusion applies to all types of flavored ENDS.

Balancing Known Risks to Youth with a Potential Benefit to Adults

Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new flavored ENDS product, the risk of youth initiation and use is substantial, given the clearly documented evidence described above. In order for marketing of a new flavored ENDS product to be found APPH, an applicant would have to show that the significant risk to youth could be overcome by likely benefits substantial enough such that the net impact to public health would be positive, taking into account all relevant evidence and circumstances, including whether there are effective limitations on youth access.

Potential benefit of new flavored ENDS

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers.[57] However, whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered on a case-by-case basis during the course of FDA's scientific review of a PMTA.

FDA also considers the potential that current cigarette smokers may experience a reduction in health risks if they switch completely to an ENDS, or if they use both products but substantially reduce their cigarette smoking. For a flavored ENDS product, assuming that the evaluation of the product shows the likelihood for lower HPHC exposure, then to demonstrate the likely individual and population benefit, applicants must demonstrate that current smokers are likely to start using the new ENDS product exclusively or predominantly (e.g., dual use with a significant smoking reduction).[64]

Behavioral evidence appropriate to demonstrate the potential benefit to smokers

FDA's PMTA review includes an evaluation of any potential benefits of the product for the likely users, such as a possible reduction in health risks. In general, as FDA stated in its guidance for PMTAs for ENDS,[xx] an assessment of how a new product may be used by current smokers can be derived from a

[xx] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

variety of sources. FDA may consider direct behavioral evidence on the specific products under review or indirect evidence derived from studies of behavioral intentions; pharmacological studies of nicotine delivery, abuse liability, and/or use topography; and bridging from studies based on comparable products. Further, in the case of a flavored ENDS product, to demonstrate that the marketing of the new product is APPH, the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk of youth uptake and use posed by the flavored ENDS product.

Section 910(c)(5) of the FD&C Act provides that determining whether marketing of a new tobacco product is APPH shall, when appropriate, be based on "well-controlled investigations, which may include one or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." FDA believes well-controlled investigations are "appropriate" for demonstrating that permitting the marketing of specific flavored ENDS would be APPH in the face of the significant risks to youth of flavored ENDS. One type of well-controlled investigation that could effectively demonstrate a potential benefit of a flavored ENDS product would be an RCT. In addition, as CTP has previously described,[xxi] another well-controlled investigation that could serve as an alternative to conducting an RCT to demonstrate adequate benefit is a longitudinal cohort study.

For flavored ENDS, the known and substantial risk to youth in particular is high. Therefore, to overcome the risk to youth and show a net population health benefit, the applicant must demonstrate potential benefits to smokers from marketing such products using particularly strong evidence – including both robust study design and methods and the strength of the study results. In other words, because the potential benefit to adults is gained through its impact on smoking behavior, such evidence should be provided to demonstrate that a benefit of a new product is significant enough to overcome the risk to youth. In particular, such evidence should permit FDA to assess whether there is any added or incremental benefit to a flavored ENDS product over a tobacco flavored variety in facilitating smokers completely switching or significantly reducing their smoking. If there is no evidence of such an incremental benefit, then there would be no justification to authorize such products, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note, whereas this evidence should be submitted for such a product to be found APPH, it may not be sufficient: having established the benefit to adults, applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization. As it relates to the risk to youth, for example, this assessment includes evaluating the appropriateness of the proposed marketing plan.[xxii]

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS products. Our substantive review of PMTAs for ENDS and our completion of numerous scientific reviews over the last 10 months have deepened our understanding of the APPH evaluation with respect to behavior. These reviews have clarified the position that the expectations for scientific evidence related to potential adult benefit can vary based on demonstrated risk to youth. Although indirect evidence or

[xxi] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

[xxii] Limiting youth access and exposure to marketing is a critical aspect of product regulation. It is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced. However, to date, none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use. Similarly, we are not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS. Accordingly, for the sake of efficiency, the evaluation of the marketing plans in applications will not occur at this stage of review.

bridged data from the literature may still be appropriate for many new products, including tobacco-flavored ENDS, robust and direct evidence demonstrating potential benefit has been needed when the known risks are high as with all flavored ENDS products. At the same time, we have learned from experience that, in the absence of strong direct evidence, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions--the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive. In fact, the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due, at least in part, to differences in the products studied. Therefore, given the state of the science on flavored ENDS, and the known risks to youth, direct product-specific evidence should be submitted.

In order to adequately assess whether such an added benefit has been demonstrated, FDA has determined that product-specific[xxiii] evidence should be submitted to enable a comparison between the applicant's new flavored products and an appropriate comparator tobacco-flavored product (both ENDS) in terms of their impact on tobacco use behavior among adult smokers. Consistent with section 910(c)(5), this evidence could be generated using either an RCT design or longitudinal cohort study design.

Although CTP will consider other types of evidence, we currently believe other types of evidence, including the types mentioned below, would not likely be sufficiently robust or direct in providing evidence as to the impact of the new ENDS on adult switching or cigarette reduction. Uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point. In addition, the transition from smoking to exclusive ENDS use typically involves a period of dual use. Therefore, evaluating the behavioral outcomes needed to show any benefit of the product requires observing the actual behavior of users over time. With both RCT and cohort study designs, enrolled participants are followed over a period of time, with periodic and repeated measurement of relevant outcomes.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to retrospect on their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior. Moreover, the general scientific literature, though informative for evaluation of some types of products, is not adequate to address this assessment because it does not provide product-specific information. This is because the effectiveness of a product in promoting switching among smokers arises from a combination of its product features—including labeled characteristics like flavor and nicotine concentration—as well as the sensory and subjective experience of use (taste, throat hit,

[xxiii] By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

nicotine delivery), and can also be influenced by how the device itself looks and feels to the use.

While RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity; cohort studies enable stronger generalizability because conditions are closer to real-world. We are aware of these as trade-offs and generally do not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new or appropriate comparator product tobacco-flavored ENDS and flavored products on adult smokers' tobacco use behavior over time[xxiv]; include outcomes related to ENDS use and smoking behavior to assess switching and/or cigarette reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the applicant's in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[xxv] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

Data from one of these studies could support a benefit to adult users if the findings showed that, compared to the new tobacco-flavored product, use of (each) new flavored product is associated with greater likelihood of either of these behavioral outcomes for adult smokers: (1) complete switching from cigarettes to exclusive new product use or (2) significant reduction in cigarettes per day (CPD).

Conclusion

The known and substantial risk to youth posed by flavored ENDS means that applicants will need a particularly reliable and robust evidence demonstrate a potential for benefit to adult smokers that could justify that risk. Based on our current understanding, a demonstration with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS. That would depend on both the type of evidence presented—whether the evidence is sufficiently reliable and robust—and the findings from the evidence. However, if an application does not contain sufficiently reliable and robust evidence, as discussed in this memo, FDA will be more likely to conclude that the application has not demonstrated the potential benefit.

[xxiv] This could include studies that are long-term (i.e., six months or longer). In FDA's (2019) Guidance to Industry, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems", FDA has previously stated that it did not expect that applicants would need to conduct long-term studies to support an application for ENDS. Because the behavior change of interest (switching or cigarette reduction) occurs over a period of time, it is possible that to observe these outcomes, investigators designing these studies may decide to follow participants over a period of six months or longer.

[xxv] Bridging is discussed in FDA's 2019 Guidance to Industry cited above (fn xxiv).

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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File
From: FOR	Anne Radway, M.S. Associate Director Division of Regulatory Project Management Office of Science Rosanna Beltre -S Digitally signed by Rosanna Beltre -S Date: 2021.08.18 14:26:09 -04'00'
Through:	Matthew Holman, Ph.D. Director Office of Science Digitally signed by Matthew R. Holman -S Date: 2021.08.18 14:29:22 -04'00'
Subject:	Addendum to Approach to PMTAs[1] for Non-Tobacco Flavored ENDS[2] not in Substantive Scientific Review (Phase III)

Background

As of September 9, 2020, FDA commenced review of premarket applications for electronic nicotine delivery systems (ENDS) products on the market as of August 8, 2016; applicants were required by a court order to submit applications to FDA by this date. On July 9, 2021 (and July 28, 2021 addendum), OS established a plan to effectively manage flavored[3] ENDS PMTAs not in Phase III, substantive scientific review, by applying a standard for evidence necessary to demonstrate a potential benefit to adult smokers of flavored ENDS. This addendum addresses the approach used to identify ENDS to undergo this review.

Discussion

FDA review of flavored ENDS as described in PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult Smokers memo (signed August 17, 2021) excludes tobacco and menthol. For Appendix A, tobacco-flavored ENDS, and Appendix B, menthol-flavored ENDS, we evaluated the list of all characterizing flavors provided by ENDS e-liquid manufacturers[4] and identified those characterizing flavors that we considered to be solely tobacco or menthol. Flavor combinations were omitted. For example, in Appendix A, Kentucky Tobacco flavor was interpreted as tobacco only, considering this is a blend type not a flavor. Any characterizing flavor that implied addition of flavors other than tobacco (e.g., Tropical Tobacco) was not included in this appendix. For Appendix B, we used a similar approach, we looked at all the

[1] Premarket Tobacco Product Applications
[2] Refers to open e-liquids, closed e-liquids, and closed e-cigarettes containing non-tobacco flavored e-liquid
[3] Throughout this memo, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.
[4] An archive query was used to identify all the flavors captured in the characterizing flavor field.

flavors listed in the characterizing flavors field and identified any flavor we considered to be menthol only, meaning that if a product listed a characterizing flavor such as "tropical menthol", this product was not included in Appendix B. Because of spelling variability and the use of different languages, we expanded the list to also include products for which tobacco or menthol was misspelled or used other descriptors such as smooth to describe the flavor. Other menthol variants such as wintergreen and frost were not included in Appendix B. Given the limitations of the archive data quality and sole use of a single field to determine the characterizing flavor, both Appendix A and B may not be an exhaustive list. The remaining flavored ENDS in PMTA bundles received by September 9, 2020, that have not started substantive scientific review, are subject to a streamlined review for evidence to demonstrate benefit to adult smokers.

Appendix A: Characterizing Flavors Determined to be Tobacco

Natural	Latakia	Turkish Bold
Tobacco	Latakia – Flavor	Turkish Flavor
7 Leaf	Latakia tobacco	Turkish Oriental Flavor
7 Leaf Tobacco	Latakia Tobacco	Turkish, Smooth
7 Tobacco	Mild Tobacco	Turkish Tob
American Blend	Mild tobacco flavor	Turkish tobacco
American Blend Tobacco	Native Tobacco	Turkish Tobacco
American tobacco	Oriental Tobacco	Turkish TObacco
American Tobacco	Original	TURKISH TOBACCO
American tobacco flavor	Pipe tobacco	Turkish Type
American tobacco flavor	Pipe Tobacco	usa blend
American Tobacco-USA Blend	Pipe Tobcco	USA Blend
American USA Blend	Pureleaf Tobacco	USA Blend Tobacco
American Virginian Flavor	Pure Tobacco	USA Blend Tobacco E Juice
Americna Blend	Regular	USA Blend Tobacco Flavor
Blended Tob	REGULAR TOBACCO	USA Blend Tobacco Flavor.
Blended Tobacco	REGULAR TOBACCO MAX	USA Tobacco
Cigar tobacco	Smooth	VirginaTobacco
Cigar Tobacco	SMOOTH	Virgina Tobacco
Classic	Smooth Tob	Virginia
Classic American tobacco	Smooth Tobacco	Virg inia
Classic Tobacco	Toacco	Virginia Blend
Cuban Cigar	tobacco	Virginia fire cured
CUBAN CIGAR	Tobacco	Virginia Fire Cured
CUBAN CIGAR MAX	Tobacco	Virginia Fire Cured ...
Cubano	TOBACCO	Virginia Fire Cured Tobacco
CUBANO	Tobacco 1	Virginia Fire Cured Tobacoo
Cubano Cigar	Tobacco Flav	Virginia Flavor
CUBANO MAX	Tobacco Flavor	Virginia Flue Cured
Cuban Tobac	Tobacco Flavoring	Virginia Flue Cured Type A
Cuban tobacco	Tobacco Pouch	Virginia Long Cut
Cuban Tobacco	Tobacco Pouch Full	Virginia Slim
Dark Mild Tobacco	Tobacco USA Blend	Virginia tobacco
Dry-aged Middle Eastern tobacco	Tobacco Virginia	Virginia Tobacco
Dryleaf Tobacco	Tobacco Virginia Flue Cured	VIRGINIA TOBACCO
Dry Tobacco	Tobacco Western Cigarette	VIRGINIA TOBACCO MAX
Flue Cured Flavor	Top Leaf Tobacco	Western
Flue Cured Tobacco	Traditional tobacco	Western Blend
Full Tobacco	Traditional Tobacco	Western Blend tobacco
Havanah Tobacco	Turkish	Western Flavor
Havana Leaf	TURKISH	Western, Smooth
Havana tobacco	Turkish Blend	Western Tobacco
Havana Tobacco	TURKISH BLENDED	

Appendix B: Characterizing Flavors Determined to be Menthol

100ml Menthol Tobacco .00nic 70/30 PGVG	Menthol Chill
100ml Menthol Tobacco .03nic 70/30 PGVG	Menthol Cigarette
100ml Menthol Tobacco .06nic 70/30 PGVG	Menthol Cool
100ml Menthol Tobacco .09nic 70/30 PGVG	Menthol Drops
100ml Menthol Tobacco .12nic 70/30 PGVG	Menthol Eucalyptus
100ml Menthol Tobacco .15nic 70/30 PGVG	Menthol Extreme
100ml Menthol Tobacco .18nic 70/30 PGVG	Menthol Flavor
100ml Menthol Tobacco .21nic 70/30 PGVG	Menthol Heaven
100ml Menthol Tobacco .24nic 70/30 PGVG	Menthol High- VG
100ml Menthol Tobacco .30nic 70/30 PGVG	Menthol Ice
100ml Menthol Tobacco .35nic 70/30 PGVG	Menthol ICE
100ml Menthol Tobacco .40nic 70/30 PGVG	Menthol Ice Tobacco
100ml Menthol Tobacco .45nic 70/30 PGVG	Menthol Kings
100ml Menthol Tobacco .50nic 70/30 PGVG	Menthol Liquid
15ml Menthol Tobacco .00nic 70/30 PGVG	Menthol Liquid (PG)
15ml Menthol Tobacco .03nic 70/30 PGVG	Menthol Lite
15ml Menthol Tobacco .06nic 70/30 PGVG	Menthol Madness
15ml Menthol Tobacco .09nic 70/30 PGVG	Menthol Max
15ml Menthol Tobacco .12nic 70/30 PGVG	MENTHOL MAX
15ml Menthol Tobacco .15nic 70/30 PGVG	Menthol Mint
15ml Menthol Tobacco .18nic 70/30 PGVG	Menthol Pipe
15ml Menthol Tobacco .21nic 70/30 PGVG	Menthol Solution
15ml Menthol Tobacco .24nic 70/30 PGVG	Menthol Tob
30ml Menthol Tobacco .00nic 70/30 PGVG	Menthol Tobacclo
30ml Menthol Tobacco .03nic 70/30 PGVG	Menthol tobacco
30ml Menthol Tobacco .06nic 70/30 PGVG	Menthol Tobacco
30ml Menthol Tobacco .09nic 70/30 PGVG	Menthol Tobacco Like Flavor
30ml Menthol Tobacco .12nic 70/30 PGVG	Menthol Tobbacco
30ml Menthol Tobacco .15nic 70/30 PGVG	Menthol Type
30ml Menthol Tobacco .18nic 70/30 PGVG	Menthol, 120ml CRC Bottle, 0mg Nic
30ml Menthol Tobacco .21nic 70/30 PGVG	Menthol, 120ml CRC Bottle, 3mg Nic
30ml Menthol Tobacco .24nic 70/30 PGVG	Menthol, 120ml CRC Bottle, 6mg Nic
30ml Menthol Tobacco .30nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 0mg Nic
30ml Menthol Tobacco .35nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 12mg Nic
30ml Menthol Tobacco .40nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 18mg Nic
30ml Menthol Tobacco .45nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 24mg Nic
30ml Menthol Tobacco .50nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 36mg Nic
60ml Menthol Tobacco .00nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 3mg Nic
60ml Menthol Tobacco .03nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 48mg Nic
60ml Menthol Tobacco .06nic 70/30 PGVG	Menthol, 30ml CRC Bottle, 6mg Nic
60ml Menthol Tobacco .09nic 70/30 PGVG	Menthol, 60ml CRC Bottle, 0mg Nic
60ml Menthol Tobacco .15nic 70/30 PGVG	Menthol, 60ml CRC Bottle, 3mg Nic
60ml Menthol Tobacco .18nic 70/30 PGVG	Menthol, 60ml CRC Bottle, 6mg Nic
60ml Menthol Tobacco .21nic 70/30 PGVG	Menthol, Mint and Tobacco

Appendix B: Characterizing Flavors Determined to be Menthol (continued)

60ml Menthol Tobacco .24nic 70/30 PGVG	MB Type Blend Menthol
60ml Menthol Tobacco .30nic 70/30 PGVG	Medium Menthol
60ml Menthol Tobacco .35nic 70/30 PGVG	Mega Menthol
60ml Menthol Tobacco .40nic 70/30 PGVG	Megan's Menthol
60ml Menthol Tobacco .45nic 70/30 PGVG	Menthol
60ml Menthol Tobacco .50nic 70/30 PGVG	menthol
American Blend Menthol	Menthol
American Menthol	Menthol
Blue Chip-Pure Menthol-	Menthol (Liquid)
Cigarrett Menthol	MENTHOL 50/50
Classic Line/Menthol Tobacco	MENTHOL 60/40
Classic Menthol	Menthol and Tobacco
Clear and Menthol	Menthol Blend
Cloud Walker Menthol	Menthol Bold
Crazy Menthol	Menthol, tobaacco
Cream De La Menthe	Menthol, Western
Cream de Menthe	Menthol, Western Tobacco
CREAM DE MENTHE	Menthol/Mint
Cream De Menthol	Mentholated Tobacco
Cream Dementhe	Mentholicious
Creame de Menthe	Mentho-Mint
Creamy Menthol	Methol
Crème de menthe	Mightly Menthol
Creme De Menthe	Mighty Menthol
Creme de Menthe II Flavor	Mild Menthol
Double Menthol	Minty Menthol
Double Menthol Tobacco	Mystic Menthol
Flavor Vapors | FV Menthol Lights	Natural Menthol
Flavor Vapors | FV Menthol Regular	natural menthol, orbit
Flavor Vapors | Menthol Burst (Coiled)	Organic Menthol
Flavor Vapors | Menthol Mint Blast	Pure Menthol
Fresh Menthol	Ry and Menthol
Half Menthol	RY and Menthol
Heavy Menthol	Smooth Menthol
House Menthol	Smooth Menthol Tobacco
Just Menthol	Spearmenthol
Kool Menthol	Stormcloud menthol
LIGHT MENTHOL	Tobacco and Menthol
Major Menthol, 120ml CRC Bottle, 0mg Nic	Tobacco menthol
Major Menthol, 120ml CRC Bottle, 3mg Nic	Tobacco Menthol
Major Menthol, 120ml CRC Bottle, 6mg Nic	Tobacco Menthol Cigarette
Major Menthol, 30ml CRC Bottle, 0mg Nic	Tobacco with Heavy Menthol
Major Menthol, 30ml CRC Bottle, 12mg Nic	Tobacco with Medium Menthol
Major Menthol, 30ml CRC Bottle, 18mg Nic	Tobacco with Menthol

Appendix B: Characterizing Flavors Determined to be Menthol (continued)

Major Menthol, 30ml CRC Bottle, 24mg Nic	Tobacco with Mild Menthol
Major Menthol, 30ml CRC Bottle, 36mg Nic	Tobacco, Menthol
Major Menthol, 30ml CRC Bottle, 3mg Nic	Traditional Menthol
Major Menthol, 30ml CRC Bottle, 48mg Nic	Turkish Menthol
Major Menthol, 30ml CRC Bottle, 6mg Nic	USA Blend Tobacco, Menthol
Major Menthol, 60ml CRC Bottle, 0mg Nic	USA Menthol
Major Menthol, 60ml CRC Bottle, 3mg Nic	USA Menthol E Juice
Major Menthol, 60ml CRC Bottle, 6mg Nic	Virginia Slim Menthol
Manthol	Western, Menthol
Marbo Menthol	Western, Menthol Liquid (PG)
Marlboro Menthol	Western, Menthol, Smooth
Menthol, Smooth	

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File
From:	Benjamin Apelberg, PhD Deputy Director Office of Science Digitally signed by Benjamin Apelberg -S Date: 2021.08.25 12:28:45 -04'00'
Through:	Matthew R. Holman, PhD Director Office of Science Digitally signed by Matthew R. Holman -S Date: 2021.08.25 13:57:58 -04'00'
Subject:	Rescission of August 17, 2021, Memorandum re PMTA[i] Review: Evidence to Demonstrate Benefit of Flavored[ii] ENDS[iii] to Adult Smokers

This memorandum rescinds the August 17, 2021, Memorandum re: PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult Smokers. The Agency has reconsidered the process for FDA's PMTA flavored ENDS reviews and has determined that it will not consider or rely on the August 17, 2021, memo as a supporting document in that process. Therefore, the August 17, 2021, memo is no longer needed.

[i] Premarket Tobacco Product Application

[ii] *Flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

[iii] Electronic Nicotine Delivery System