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Given the above, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA. Instead, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. FDA also regularly posts additional resources for applicants, such as webinars and application tips, on CTP's website and social media.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File	
From:	Anne Radway, M.S. Associate Director Division of Regulatory Project Management Office of Science	Digitally signed by Anne M. Radway -S Date: 2022.11.22 12:55:08 -05'00'
Through:	Benjamin Apelberg, Ph.D. Acting Office Director Office of Science	Digitally signed by Benjamin Apelberg -S Date: 2022.11.22 13:07:12 -05'00'
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 court order to submit applications to FDA by this date. On July 9, 2021 (and addenda dated July 28, 2021, and August 8, 2021), OS established a plan to effectively manage non-tobacco and non-menthol flavored 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 (i.e., "FE review"). This addendum describes the following updates to the FE review process: 1) the inclusion of menthol-flavored ENDS PMTAs; 2) expanding the scope of review to include the application's proposed marketing restrictions and mitigation measures; and 3) the continuation of this review process to include applicable flavored ENDS PMTAs received after September 9, 2020.

Discussion

Menthol-Flavored ENDS PMTAs

To date, menthol-flavored ENDS PMTAs have been excluded from the FE review process, as CTP deliberated over the most appropriate scientific approach for reviewing these products. FDA has concluded that the existing scientific literature does not demonstrate a benefit to adult smokers that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS. Thus, the approach to the APPH analysis for menthol-flavored ENDS is the same as for other non-tobacco flavored ENDS, in that, to overcome the risk to youth, an applicant must provide evidence demonstrating their menthol-flavored ENDS products provide an added benefit for adult smokers relative to tobacco-flavored ENDS.

As the scientific approach to menthol-flavored ENDS is now the same as for other non-tobacco-flavored ENDS, moving forward, menthol-flavored ENDS will also be subject to FE review and the applicable rationale in full substantive review. To implement this change, OS will advise all review staff that for FE review they are to include menthol-flavored ENDS products:

[1] Premarket Tobacco Product Applications

[2] Refers to open e-liquids, closed e-liquids, and closed e-cigarettes containing non-tobacco flavored e-liquid

- The definition of "flavored ENDS products" will include all non-tobacco flavored ENDS products[3] (this typically appears in a footnote in the TPL reviews); and
- The supporting literature documenting the risks to youth and benefits to adults, respectively, that is cited in the FE TPL review template will be applicable to, and inclusive of, menthol-flavored ENDS products.

OS will ensure that staff have knowledge of these changes and ensure that the changes to FE reviews are implemented moving forward. These changes will be effective immediately.

Marketing Restrictions and Mitigation Measures

To date, the scope of FE review has been limited to the data relevant to demonstrating the added benefit to adult smokers compared to tobacco-flavored ENDS and did not include the application's marketing plan. At this time, we are adjusting the scope of FE review. In particular, although we have thus far concluded that restrictions on advertising and promotion and sales access would not be adequate to mitigate the risk to youth from flavored ENDS sufficiently to warrant review of an application that does not include robust and reliable evidence of adult benefit, given the concerns expressed by a number of federal courts, as part of targeted review, we are now reviewing all applicant-proposed marketing restrictions and mitigation measures to ensure that there are no other types of novel or materially different proposals, such as device access restrictions, that have the potential to mitigate the substantial risk to youth from flavored ENDS sufficiently to decrease the magnitude of adult benefit needed to show APPH. [4]

Moving forward, FE review will include a question to evaluate the application's proposed marketing restrictions and mitigation measures to determine if they propose any novel or materially different measures (e.g., device access restrictions) from those that FDA has considered and found insufficient. In the event such a novel measure (e.g., device access restriction) is identified, the application will be pulled out of FE review and put in the queue for full substantive scientific review.

FE Review of Applications Received After September 9, 2020

The initial memo and addenda describe a plan to employ FE review to the pending queue of non-tobacco, non-menthol[5] flavored ENDS PMTAs received by September 9, 2020, but not yet under scientific review. With this addendum, we update this plan to broaden the scope of PMTAs subject to FE review to also include those flavored ENDS (menthol and other non-tobacco flavors) received after September 9, 2020.

[3] The term "flavored ENDS" also includes 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.

[4] See *Prohibition Juice Co. v. FDA*, 45 F.4th 8, 24-25 (D.C. Cir. 2022); *Wages & White Lion Investments, L.L.C.,* 41 F.4th 427 (5th Cir. 2022) (pet. for reh'g filed (Sept. 1, 2022); *Bidi Vapor LLC v. FDA*, No. 21-13340, F.4th, 2022 WL 3594073 (11th Cir. Aug. 23, 2022).

[5] Although the original memo and addenda excluded menthol ENDS from the scope of FE review, we are now including menthol ENDS as described above.