The following memorandum "ENDS Containing Non-Tobacco Flavored E-Liquid: Approach to PMTAs not in Substantive Scientific Review (Phase III)", was finalized on July 09, 2021. This memorandum characterizes a plan to manage review of non-tobacco flavored ENDS products as "fatal flaw review," which oversimplifies CTP's process of review for flavored ENDS products. Therefore, this explanatory note clarifies that the term should be "flavored ENDS review."

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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 <u>also regularly posts additional resources</u> for applicants, such as webinars and application tips, on <u>CTP's website</u> and <u>social media</u>.



Memorandum

То:	File		
From:	Anne Radway, M.S. Associate Director Division of Regulatory Project Management Office of Science For 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. 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 memorandum³, 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).

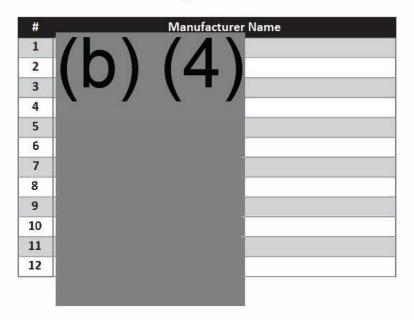
Considering the large number of applications that remain to be reviewed by the September 9, 2021 deadline, OS will conduct a Fatal Flaw review of PMTAs not in Phase III for non-tobacco flavored ENDS products. The Fatal Flaw review is a simple review in which the reviewer examines the submission to identify 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 twelve⁴ manufacturers with the largest number of pending PMTAs not in Phase III⁵ 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.

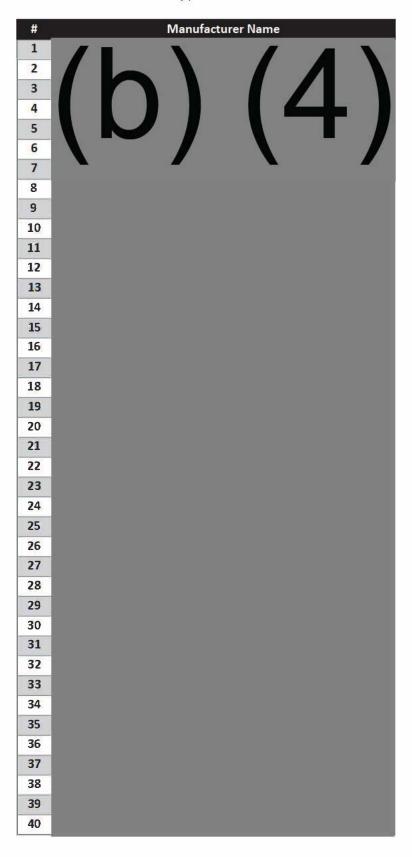
⁴ These applications represent 85% of all pending PMTA applications.

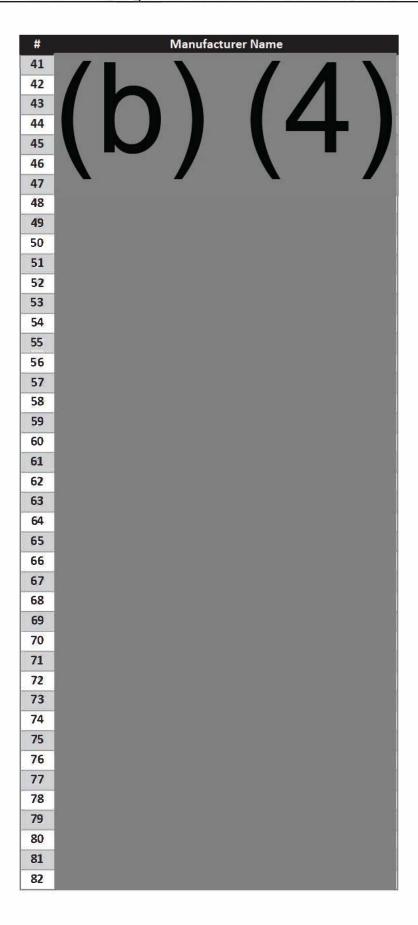
⁵ These will be the same manufacturers/PMTAs as identified for prioritized Filing Reviews in the June 30, 2021, memorandum.

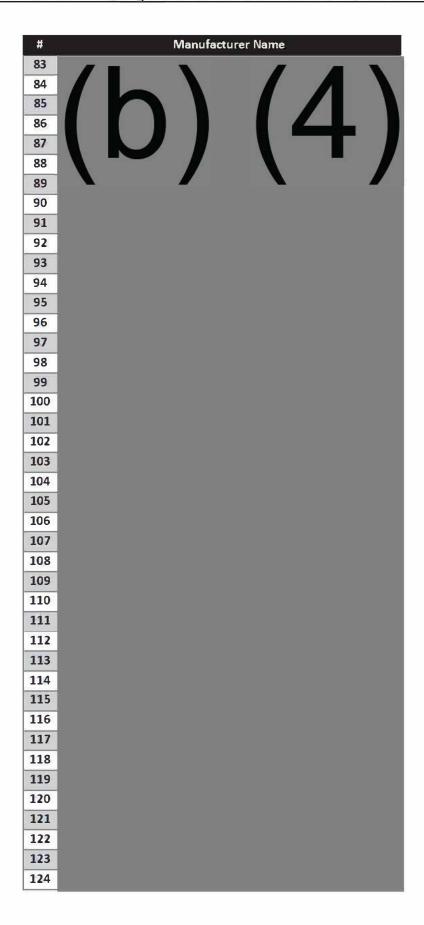
Appendix A

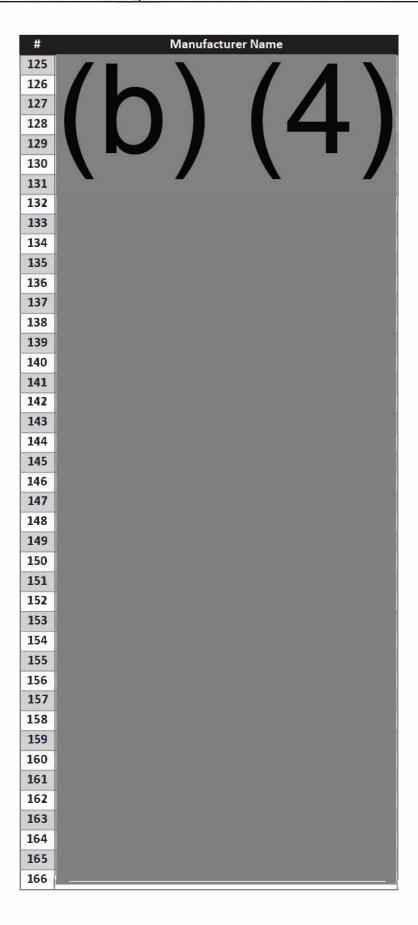


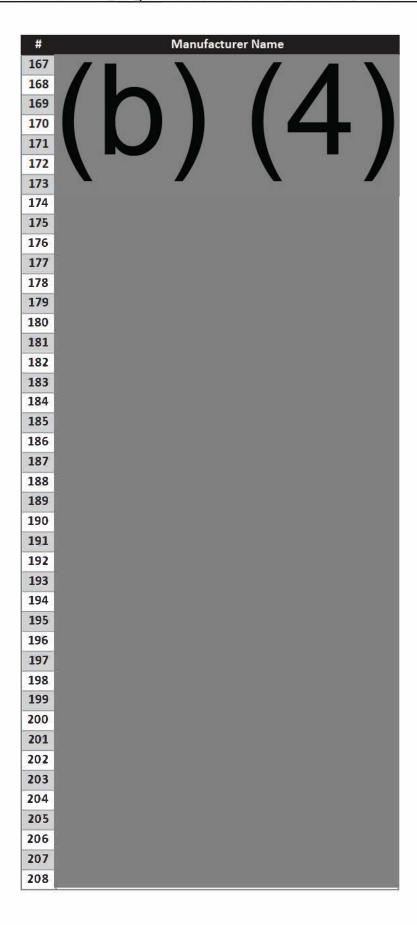
Appendix B











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