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."

This document has been posted in compliance with the FOIA Improvement Act of 2016, which requires agencies to make certain records that have been requested three or more times publicly available. It provides a snapshot of CTP's internal thinking on certain aspects of tobacco regulatory science. The information it contains is subject to change, such as based on changes in policy, the regulatory framework, or regulatory science. It is not binding on FDA or the public. It may have been withdrawn or superseded after it was issued or may otherwise be outdated. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in reviews particular to each application.

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 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

#	Manufacturer Name
1	(b) (4)
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

Appendix B

#	Manufacturer Name
1	(b) (4)
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	

#	Manufacturer Name
41	(b) (4)
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	
61	
62	
63	
64	
65	
66	
67	
68	
69	
70	
71	
72	
73	
74	
75	
76	
77	
78	
79	
80	
81	
82	

#	Manufacturer Name
83	(b) (4)
84	
85	
86	
87	
88	
89	
90	
91	
92	
93	
94	
95	
96	
97	
98	
99	
100	
101	
102	
103	
104	
105	
106	
107	
108	
109	
110	
111	
112	
113	
114	
115	
116	
117	
118	
119	
120	
121	
122	
123	
124	

#	Manufacturer Name
125	(b) (4)
126	
127	
128	
129	
130	
131	
132	
133	
134	
135	
136	
137	
138	
139	
140	
141	
142	
143	
144	
145	
146	
147	
148	
149	
150	
151	
152	
153	
154	
155	
156	
157	
158	
159	
160	
161	
162	
163	
164	
165	
166	

#	Manufacturer Name
167	(b) (4)
168	
169	
170	
171	
172	
173	
174	
175	
176	
177	
178	
179	
180	
181	
182	
183	
184	
185	
186	
187	
188	
189	
190	
191	
192	
193	
194	
195	
196	
197	
198	
199	
200	
201	
202	
203	
204	
205	
206	
207	
208	

#	Manufacturer Name
209	(b) (4)
210	
211	
212	
213	
214	
215	
216	
217	
218	
219	
220	
221	
222	
223	
224	
225	
226	
227	
228	
229	
230	
231	
232	
233	
234	
235	
236	
237	
238	
239	
240	
241	
242	
243	
244	
245	
246	
247	
248	
249	
250	

#	Manufacturer Name
251	(b) (4)
252	
253	
254	
255	
256	
257	
258	
259	
260	
261	
262	
263	
264	
265	
266	
267	
268	
269	
270	
271	
272	
273	
274	
275	
276	
277	
278	
279	
280	
281	
282	
283	
284	
285	
286	
287	
288	
289	
290	
291	
292	

#	Manufacturer Name
293	(b) (4)
294	
295	
296	
297	
298	
299	
300	
301	
302	
303	
304	
305	
306	
307	
308	
309	
310	
311	
312	
313	
314	
315	
316	
317	
318	
319	
320	
321	
322	
323	
324	
325	
326	
327	
328	
329	
330	
331	
332	
333	
334	

#	Manufacturer Name
335	(b) (4)
336	
337	
338	
339	
340	
341	
342	
343	
344	
345	
346	
347	
348	
349	
350	
351	
352	
353	
354	
355	
356	
357	
358	
359	
360	
361	
362	