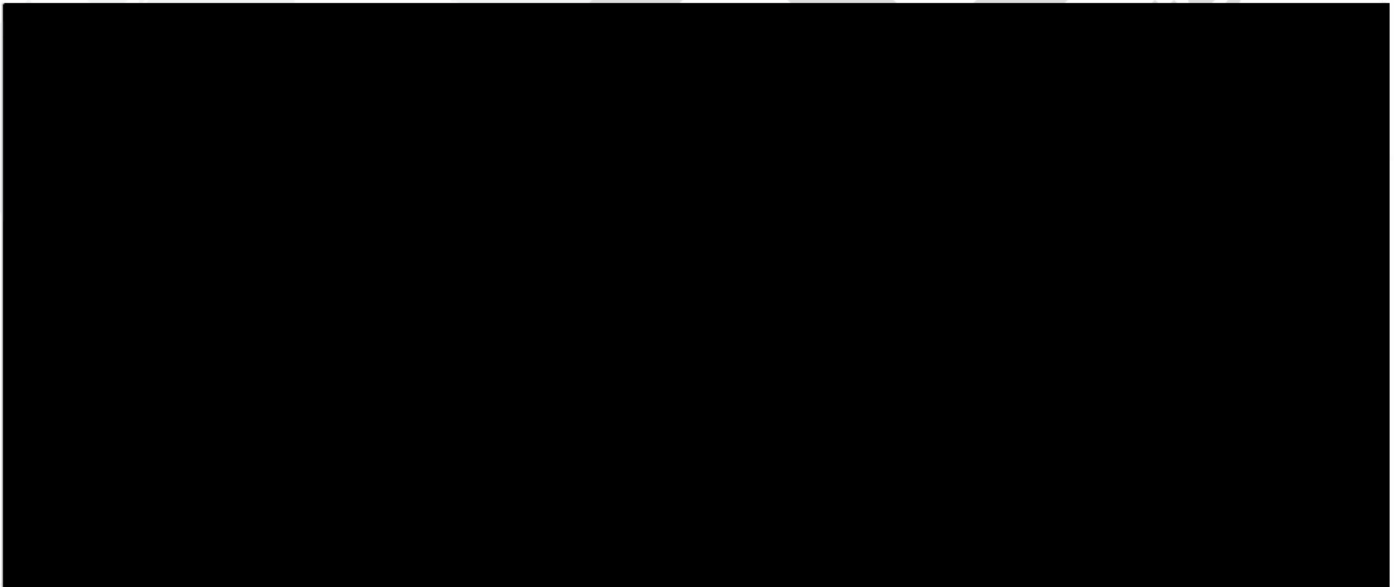


Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

DRAFT GUIDANCE



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products





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Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist persons submitting premarket tobacco product applications (PMTAs) for electronic nicotine delivery systems (ENDS) under section 910 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387j). This guidance explains, among other things:

- Products to which this guidance applies;
- When a PMTA is required;
- How FDA intends to review an ENDS PMTA;
- What information the FD&C Act requires you to submit in a PMTA; and
- What information FDA recommends you submit in an ENDS PMTA to show whether permitting such new tobacco product to be marketed is appropriate for the protection of the public health.

FDA's draft guidance for industry, *Applications for Premarket Review of New Tobacco Products* (draft premarket review guidance),² discusses the general procedures for submitting a PMTA, including who can submit a PMTA, and when and how PMTAs should be submitted. Please note

¹ This guidance was prepared by the Office of Science and Office of Regulations in the Center for Tobacco Products at FDA.

² When finalized, the guidance *Applications for Premarket Review of New Tobacco Products* will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Tobacco Product Guidance page at <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm>.



34 that, when finalized, this guidance’s focus on ENDS products may result in more specific
35 recommendations for an ENDS PMTA than what is contained in FDA’s draft premarket review
36 guidance.

37
38 FDA’s guidance documents, including this guidance, do not establish legally enforceable
39 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
40 be viewed only as recommendations, unless specific regulatory or statutory requirements are
41 cited. The use of the word *should* in Agency guidances means that something is suggested or
42 recommended, but not required.

43
44 **II. BACKGROUND**

45
46 The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law
47 111-31) was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the
48 authority to regulate tobacco products. Specifically, section 101(b) of the Tobacco Control Act
49 amends the FD&C Act by adding a new chapter that provides FDA with authority over tobacco
50 products. Section 901 of the FD&C Act (21 U.S.C. 387a), as amended by the Tobacco Control
51 Act, states that the new chapter in the FD&C Act (chapter IX—Tobacco Products) (21 U.S.C.
52 387 through 387t) applies to all cigarettes, cigarette tobacco, roll-your-own tobacco, and
53 smokeless tobacco and to any other tobacco products that the Secretary of Health and Human
54 Services by regulation deems to be subject to this chapter.

55
56 Concurrently with issuing this guidance, FDA is publishing a final rule, “Deeming Tobacco
57 Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the
58 Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution
59 of Tobacco Products and Required Warning Statements for Tobacco Products,” (final deeming
60 rule) to deem all products meeting the statutory definition of “tobacco product” in section 201(rr)
61 of the FD&C Act (21 U.S.C. 321(rr)), except accessories of newly deemed tobacco products, to
62 be subject to chapter IX of the FD&C Act. In the final deeming rule, FDA clarifies that all ENDS
63 (including, but not limited to, e-cigarettes, e-cigars, e-hookah, vape pens, personal vaporizers,
64 and electronic pipes) are subject to FDA’s chapter IX authorities on the effective date of the final
65 deeming rule.³ ENDS products include both the e-liquid and aerosolizing apparatus used as an
66 ENDS, whether sold as a unit or separately. Products deemed under the final deeming rule will
67 now be subject to most of the same FD&C Act provisions to which cigarettes, cigarette tobacco,
68 roll-your-own tobacco, and smokeless tobacco are subject, including premarket review
69 requirements and the adulteration and misbranding provisions. In addition, these products are
70 also subject to certain other restrictions set out in the final deeming rule and may be subject to
71 other requirements or restrictions established in future regulations.

72
73 Under section 910 of the FD&C Act, persons wanting to market a new tobacco product (one that
74 was not commercially marketed in the United States on February 15, 2007, or any modified

³ If an ENDS manufacturer wishes to make a cessation claim or otherwise market its product for therapeutic purposes, the company must submit an application for their ENDS to be marketed as a medical product. Please see section IV.B.1 for further discussion.



75 tobacco product that was commercially marketed after February 15, 2007) must first obtain an
76 order to do so (referred to in this guidance as a marketing order) under section 910(c)(1)(A)(i)
77 unless a report pursuant to section 905(j) of the FD&C Act has been submitted for the new
78 tobacco product and FDA has issued an order under section 910(a)(2) that the new tobacco
79 product is substantially equivalent to a tobacco product commercially marketed in the United
80 States as of February 15, 2007 (the 905(j) pathway), or the new tobacco product is exempt from
81 the substantial equivalence requirements. When a new product is not found to be substantially
82 equivalent to an appropriate predicate product or exempt from the substantial equivalence
83 requirements, you must submit a PMTA under section 910(b) and receive a marketing order
84 under section 910(c)(1)(A)(i) prior to marketing the product.

85
86 All newly deemed products that meet the definition of a “new tobacco product,” including
87 ENDS, are subject to the premarket requirements in sections 910 and 905 (21 U.S.C. 387j and
88 387e) of the FD&C Act. Given the limited availability of valid predicates for use in the
89 substantial equivalence pathway, FDA expects to receive PMTA submissions from
90 manufacturers of newly deemed ENDS. Section 910(b)(1) of the FD&C Act contains
91 requirements for a PMTA submission. This guidance is intended to provide information to assist
92 applicants in submitting a sufficient level of information to obtain a marketing order under
93 section 910(c)(1)(A)(i).

94
95 To the extent that an eligible predicate product (one marketed as of February 15, 2007, or
96 previously determined to be substantially equivalent to an appropriate predicate product) is
97 available for ENDS products, and firms are interested in utilizing the 905(j) pathway to market
98 for their new ENDS tobacco products, we refer you to FDA’s relevant guidance documents
99 located at
100 [http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.h](http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm)
101 [tm](http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm).

102
103 This guidance represents FDA’s current thinking on some appropriate means of addressing the
104 premarket authorization requirements for newly deemed ENDS products.

105
106 **III. DEFINITIONS**

107
108 This section provides definitions of certain terms as they are used in this guidance document.

109
110 **A. Accessory**

111
112 The term *accessory* means any product that is intended or reasonably expected to be used with or
113 for the human consumption of a tobacco product; does not contain tobacco and is not made or
114 derived from tobacco; and meets either of the following: (1) is not intended or reasonably
115 expected to affect or alter the performance, composition, constituents, or characteristics of a
116 tobacco product; or (2) is intended or reasonably expected to affect or maintain the performance,
117 composition, constituents, or characteristics of a tobacco product but (i) solely controls moisture
118 and/or temperature of a stored product or (ii) solely provides an external heat source to initiate
119 (but not maintain) combustion of a tobacco product (21 CFR 1143.1). “Composition,” as used in



120 this definition, means the manner in which the materials, including, for example, ingredients,
121 additives, and biological organisms, are arranged and integrated.

122

123 **B. Component or Part**

124

125 Component or part means any software or assembly of materials intended or reasonably
126 expected: 1) to alter or affect the tobacco product’s performance, composition, constituents, or
127 characteristics; or 2) to be used with or for the human consumption of a tobacco product.

128 Component or part excludes anything that is an accessory of a tobacco product.

129 The following is a nonexhaustive list of examples of components or parts of ENDS (including e-
130 cigarettes): e-liquids, atomizers, batteries (with or without variable voltage), cartomizers
131 (atomizer plus replaceable fluid-filled cartridge), digital display/lights to adjust settings;
132 clearomisers, tank systems, flavors, bottles that contain e-liquids, and programmable software.

133

134 **C. Covered Tobacco Product**

135

136 The term *covered tobacco product* means any tobacco product deemed to be subject to the
137 FD&C Act under section 21 CFR § 1100.1, but excludes any component or part of a tobacco
138 product that is not made or derived from tobacco.

139

140 **D. Finished Tobacco Product**

141

142 The term *finished tobacco product* refers to a tobacco product, including all components and
143 parts, sealed in final packaging intended for consumer use. For example, an e-liquid sealed in
144 final packaging that is to be sold or distributed to a consumer for use is a finished tobacco
145 product, but in contrast, an e-liquid that is sold or distributed for further manufacturing into a
146 finished ENDS product is not itself a finished tobacco product.

147

148 **E. New Tobacco Product**

149

150 The term *new tobacco product* is defined in section 910(a)(1) of the FD&C Act as:

151

152 (A) any tobacco product (including those products in test markets) that was not
153 commercially marketed in the United States as of February 15, 2007; or

154 (B) any modification (including a change in design, any component, any part, or any
155 constituent, including a smoke constituent, or in the content, delivery or form of
156 nicotine, or any other additive or ingredient) of a tobacco product where the modified
157 product was commercially marketed in the United States after February 15, 2007.⁴

158

159 **F. Tobacco Product**

160

⁴ FDA has interpreted “as of February 15, 2007” to mean any tobacco product that was not commercially marketed in the United States on February 15, 2007. For additional discussion, see FDA’s guidance for industry *Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007*.



161 A *tobacco product* is “any product made or derived from tobacco that is intended for human
162 consumption, including any component, part, or accessory of a tobacco product (except for raw
163 materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco
164 product)” (section 201(rr) of the FD&C Act). This term does not include an article that is a drug,
165 device, or combination product as defined in the FD&C Act. The term is not limited to products
166 containing tobacco or tobacco derivatives, but also includes components, parts, or accessories of
167 tobacco products, whether they are sold for further manufacturing or for consumer use. For
168 example, e-liquids, aerosolizing apparatus, atomizers, and batteries used in ENDS are tobacco
169 products, whether they are sold to consumers for use in an ENDS or are sold for further
170 manufacturing into another product sold to a consumer.

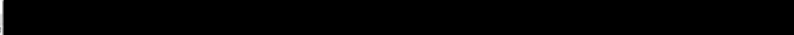
171
172 **IV. DISCUSSION**

173
174 **A. Products to Which This Guidance Applies**

175
176 There are many types of ENDS products (including, but not limited to, e-cigarettes, e-cigars, e-
177 hookah, vape pens, personal vaporizers, and electronic pipes), all of which are subject to FDA’s
178 tobacco product authorities as of the effective date of the final deeming rule because they meet
179 the definition of “tobacco product” under section 201(rr) of the FD&C Act and are not
180 accessories of newly deemed products. In addition to ENDS products themselves, components
181 and parts of ENDS products, but not their related accessories, are also subject to FDA’s
182 authority. The following is a nonexhaustive list of examples of components or parts of ENDS
183 (including e-cigarettes): e-liquids, atomizers, batteries (with or without variable voltage),
184 cartomizers (atomizer plus replaceable fluid-filled cartridge), digital display/lights to adjust
185 settings, clearomisers, tank systems, flavors, and programmable software. The ENDS category
186 includes a variety of products and, because it is a rapidly changing industry, new ENDS products
187 may be developed in the future. Currently, FDA generally considers ENDS as tobacco products
188 that use an electronic or other power source to heat e-liquids, tobacco, or other material derived
189 from tobacco.

190
191 Subsequent sections of this guidance refer to three subcategories of ENDS products:

- 192
193
 - E-liquids
 - Aerosolizing apparatus
 - ENDS products that package e-liquids and aerosolizing apparatus together

196
197 We briefly describe e-liquids and aerosolizing apparatus below and provide our
198 recommendations in section VI through VIII regarding the type of information that should be
199 submitted for these three subcategories of products. FDA recognizes that with the innovation in
200 the ENDS market, there may be ENDS products that do not fit neatly into one of these
201 categories. If you have questions about which recommendations you should follow for your
202 ENDS product, 

203
204 **1. E-Liquids**

205



206 As stated in section 201(rr) of the FD&C Act, the definition of “tobacco product” includes any
207 product made or derived from tobacco that is intended for human consumption that is not a drug
208 or device, including any component, part, or accessory of a tobacco product. Upon the effective
209 date of the deeming rule, all products meeting this definition, except for accessories of newly
210 deemed products, will be subject to FDA’s chapter IX authorities. An e-liquid that contains
211 nicotine made or derived from tobacco meets these criteria and, therefore, is subject to FDA’s
212 chapter IX authorities. For the purposes of this guidance document, *liquid nicotine* and *nicotine-*
213 *containing e-liquids* (i.e., liquid nicotine combined with colorings, flavorings, and/or potentially
214 other ingredients) are generally referred to as *e-liquids*. Liquids that do not contain nicotine or
215 other material made or derived from tobacco but that are intended or reasonably expected to be
216 used with or for the human consumption of a tobacco product also are referred to as e-liquids for
217 the purposes of this guidance document. For example, where a “zero nicotine” or “nicotine free”
218 e-liquid is intended or reasonably expected to be mixed with liquid nicotine, that e-liquid may be
219 a component or part of a tobacco product and subject to FDA’s tobacco control authorities. FDA
220 considers such e-liquids to be a tobacco product even if sold separately from an aerosolizing
221 apparatus.

222
223 2. *Aerosolizing Apparatus*

224
225 For the purposes of this guidance, *aerosolizing apparatus* refers to all components and parts
226 (together or sold separately) of an ENDS product, other than the e-liquid itself, that interact
227 directly or indirectly with e-liquid in the use of the tobacco product. For example, FDA considers
228 an e-cigarette, e-pen, e-hookah without e-liquids, or a battery sold separately (to be used with an
229 ENDS product) to be an aerosolizing apparatus.

230
231 **B. When Are PMTAs Required?**

232
233 1. *Considerations for All Applicants*

234
235 Section 910 of the FD&C Act requires a marketing order for new tobacco products. At this time,
236 FDA intends to limit enforcement of the requirements of section 910 to finished tobacco
237 products, including components and parts of ENDS products sold or distributed separately for
238 consumer use. FDA does not, at this time, intend to enforce these requirements for components
239 and parts of newly deemed products that are sold or distributed solely for further manufacturing
240 into finished tobacco products, and not sold separately to the consumer. For example, an e-liquid
241 that is sold or distributed for further manufacturing into a finished ENDS product is not itself a
242 finished tobacco product and, at this time, FDA does not intend to enforce against such e-liquids
243 that are sold or distributed without a marketing order. In contrast, an e-liquid sealed in final
244 packaging that is to be sold or distributed to a consumer for use is a finished tobacco product.
245 FDA intends to enforce against such e-liquids that are sold or distributed without a marketing
246 order.

247
248 If an ENDS product is marketed for tobacco cessation or for any other therapeutic purpose, the
249 product will be regulated as a drug or device, rather than a tobacco product, under the authorities



250 of FDA’s Center for Drug Evaluation and Research or Center for Devices and Radiological
251 Health, and appropriate approval must be sought to market a product as a drug or device.⁵

252
253 2. *ENDS Retailers Who Mix or Prepare Their Own E-Liquids or Create or*
254 *Modify Aerosolizing Apparatus from Various Components*

255
256 An ENDS retail establishment that mixes and/or prepares combinations of liquid nicotine,
257 flavors, and/or other liquids for direct sale to consumers for use in ENDS or creates or modifies
258 aerosolizing apparatus for direct sale to consumers for use in ENDS (sometimes known as a vape
259 shop) meets the definition of “tobacco product manufacturer” in section 900(20)⁶ of the FD&C
260 Act (21 U.S.C. 387(20)) and the combinations it mixes and/or prepares are “new tobacco
261 products” within the meaning of section 910(a)(1). Section 910(a)(1) defines a “new tobacco
262 product” as “any tobacco product (including those products in test markets) that was not
263 commercially marketed in the United States as of February 15, 2007,” or “any modification
264 (including a change in design, any component, any part, or any constituent, including a smoke
265 constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of
266 a tobacco product where the modified product was commercially marketed in the United States
267 after February 15, 2007.” Therefore, those establishments engaged in mixing and/or preparing
268 combinations of liquid nicotine, flavors, and/or other liquids or creating or modifying
269 aerosolizing apparatus for direct sale to consumers for use in ENDS are tobacco product
270 manufacturers and, consequently, are subject to all of the requirements applicable to
271 manufacturers.

272
273 **C. How Will FDA Review an ENDS PMTA?**

274
275 FDA will review an ENDS PMTA consistent with the requirements of section 910(c) of the
276 FD&C Act. Under section 910(c)(1)(A), FDA must act on a PMTA “as promptly as possible, but
277 in no event later than 180 days after the receipt of an application.” A PMTA must include all
278 information specified in 910(b)(1) upon submission and FDA may refuse to file incomplete
279 applications. However, FDA may request additional information about your PMTA as necessary.
280 FDA may also want to inspect your manufacturing, clinical research, or nonclinical research sites
281 to support its review of your PMTA.

282
283 Under section 910(b)(2) of the FD&C Act, FDA has the discretion, upon your request or on its
284 own initiative, to refer your PMTA to the Tobacco Product Scientific Advisory Committee
285 (TPSAC). If you wish to request that FDA refer your PMTA to TPSAC, you should include the
286 request in the cover letter of your initial PMTA submission.

287

⁵ See sections 505 (21 U.S.C. 355) (drugs) and 515 (21 U.S.C. 360e) (devices) of the FD&C Act and *Sottera, Inc. v. Food & Drug Administration*, 627 F.3d 891 (D.C. Cir. 2010).

⁶ A “tobacco product manufacturer” means “any person, including any repacker or relabeler, who manufactures, fabricates, assembles, processes, or labels a tobacco product; or imports a finished tobacco product for sale or distribution in the United States.” (Section 900(20) of the FD&C Act, 21 U.S.C. 387(20)).



288 **D. Public Health Considerations for ENDS Products**

289
290 *1. Section 910(c)(2)(A)'s Standard: A Showing That the New Tobacco*
291 *Product Is Appropriate for the Protection of the Public Health*

292
293 Section 910(c)(2)(A) of the FD&C Act requires that FDA deny PMTAs where it finds “there is a
294 lack of a showing that permitting such tobacco product to be marketed would be appropriate for
295 the protection of the public health.”⁷ We provide information in this section to assist applicants
296 in submitting an ENDS PMTA that could support a showing that the marketing of a new tobacco
297 product is appropriate for the protection of the public health. Our finding of whether there is a
298 showing that permitting this product to be marketed would be appropriate for the protection of
299 the public health must be determined with respect to the risks and benefits to the population as a
300 whole, including users and nonusers of the tobacco product, and taking into account:

- 301
302 (A) The increased or decreased likelihood that existing users of tobacco products will stop
303 using such products; and
304 (B) The increased or decreased likelihood that those who do not use tobacco products will
305 start using such products.

306
307 (Section 910(c)(4) of the FD&C Act.)

308
309 Throughout this guidance document, we recommend providing specific information pertaining to
310 different topic areas and disciplines in order to enable FDA to make a determination of whether
311 your PMTA supports a showing that the marketing of your new tobacco product is appropriate
312 for the protection of the public health. For example, knowing the full assessment of the
313 toxicological effects of your ENDS product (i.e., ingredients, components, use of the product) is
314 important to assess the health effects on users and nonusers. FDA will assess the toxicology of
315 the product to determine whether the health effects of using the product would have a
316 detrimental effect to users’ and nonusers’ health. While FDA requests this information for
317 particular topic areas and disciplines, FDA weighs all of the potential benefits and risks from the
318 product to make an overall determination of whether the product should be marketed.

319
320 Under section 910(c)(5)(A) of the FD&C Act, FDA’s finding must be determined “when
321 appropriate . . . on the basis of well-controlled investigations.” However, under section
322 910(c)(5)(B), if the Secretary determines that there exists valid scientific evidence (other than
323 evidence derived from well-controlled investigations, as described in section 910(c)(5)(A)) that

⁷ In addition, the statute provides that FDA shall deny PMTAs under section 910(c)(2) of the FD&C Act where:
(B) the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of
such tobacco product do not conform to the requirements of section 906(e);
(C) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any
particular; or
(D) such tobacco product is not shown to conform in all respects to a tobacco product standard in effect
under section 907, and there is a lack of adequate information to justify the deviation from such standard.



324 is sufficient to evaluate the new tobacco product, the Secretary may authorize that the
325 determination under the public health standard be made on the basis of such evidence.

326

327 *2. Specific Recommendations Concerning How to Support a Showing That*
328 *Marketing of the New Tobacco Product Is Appropriate for the Protection of the*
329 *Public Health*

330

331 This guidance provides recommendations regarding what FDA considers important to include in
332 an ENDS PMTA. Some of the recommendations discussed below are unique to ENDS, given the
333 differences between ENDS and previously regulated products, like combusted cigarettes. Some
334 recommendations relate to basic resource and data limitations. The following sections highlight
335 several broad categories of issues that applicants should address to help demonstrate that their
336 products are appropriate for the protection of the public health and, consequently, should be
337 authorized for marketing. Please note that this guidance's focus on ENDS products may result in
338 more specific recommendations for an ENDS PMTA than what is contained in FDA's draft
339 premarket review guidance.

340

341 a. Scientific evidence

342

343 FDA recommends that you provide a detailed explanation of how the data and information
344 provided in your PMTA support a finding that introducing your new tobacco product to the
345 market is appropriate for the protection of the public health. Given the relatively new entrance of
346 ENDS on the U.S. market, FDA understands that ENDS PMTA applicants may have limited data
347 from scientific studies and analyses. Where human toxicity may be reliably predicted from
348 nonclinical data, well-designed laboratory testing (in vitro and/or in vivo) may be the basis for
349 this evaluation. (Please refer to section X.A of this guidance to review information that FDA
350 considers when determining when scientific evidence may be used in lieu of clinical studies.)

351

352 FDA recommends that your explanation include a comparison of the new tobacco product to a
353 range of tobacco products legally on the market (i.e., either grandfathered or with a marketing
354 authorization in effect) or those products that benefit from FDA's announced compliance
355 policies at the time of your PMTA submission, including traditional combusted products (e.g.,
356 cigarettes, cigars) and a comparison between your product and other similar products within the
357 same category. To completely assess whether your PMTA supports a showing that marketing the
358 product would be appropriate for the protection of the public health, FDA will look at the
359 product in the context of the current tobacco product market. FDA can do this by understanding
360 the spectrum of risk of currently available tobacco products and assessing the new product within
361 that spectrum. As an example comparison between products within the same category, if your
362 PMTA is for an e-liquid, we recommend a comparison to other e-liquids with similar nicotine
363 content, flavors, or similar other ingredients.

364

365 Additionally, FDA understands that you may want to support certain topics in your PMTA (such
366 as toxicology) with scientific data on tobacco products other than the proposed PMTA product.
367 In this case, data from those products that are used in the same manner, under similar conditions,
368 or for the same duration and frequency may be used to support your PMTA. Whether this



369 information is appropriate depends on the specific products, the facts of the study or data, and the
370 similarity of the product to your PMTA product. You should provide justification in your PMTA
371 regarding why using evidence or data from other products to support your PMTA is appropriate
372 based on these factors and other relevant considerations. Section X of this guidance describes
373 FDA's thinking on options for manufacturers to obtain this scientific information (e.g., from
374 published literature studies).

375

376 In sections VI.H, VII, VIII, and IX, we discuss the information that FDA recommends including
377 in scientific studies and analyses to support a showing that permitting the new tobacco product to
378 be marketed would be appropriate for the protection of the public health. An applicant may
379 reference the same scientific evidence to demonstrate qualities of the tobacco product for
380 different areas and disciplines, if applicable. In section X, we discuss the types of studies and
381 research that may be appropriate to use in lieu of longitudinal clinical studies, given the
382 limitations noted above. Also, to the extent that you propose specific restrictions on sale and
383 distribution that can help support a showing that the marketing of the product is appropriate for
384 the protection of the public health, FDA may consider your product in that context and may
385 include your proposed restrictions as mandatory conditions in your marketing order. This is in
386 addition to any other restrictions that FDA may require on the sale and distribution of the
387 tobacco product, or any postmarket records and reports FDA may find necessary, as discussed in
388 section XI.

389

390 b. Nicotine exposure warnings

391

392 Section 910(b)(1)(F) of the FD&C Act requires that PMTAs include specimens of the labeling
393 proposed to be used for the new tobacco product. Warning statements are important parts of the
394 product's labeling. Given the health risks and hazards associated with exposure to e-liquids
395 (including oral, dermal, and ocular dangers), FDA recommends that, to help establish that
396 marketing a product is appropriate for the protection of the public health, labels or labeling of the
397 finished ENDS that contain nicotine include a nicotine exposure warning. Finished ENDS are
398 those products, including all components and parts, sealed in final packaging intended for
399 consumer use. FDA believes this warning is important to aid in the prevention of and/or decrease
400 the risk of inadvertent exposure to nicotine, especially by children, which could lead to acute
401 toxicity including potentially deadly nicotine poisoning. To that end, FDA recommends that the
402 nicotine exposure warning be included in specimens of the labels or labeling that are submitted.

403

404 The nicotine exposure warnings should accurately and truthfully communicate the health risks
405 and hazards of e-liquid use in a clear and simple manner. These warnings should:

406

- 407 • Be clear, conspicuous, prominent, understandable, factual, and not false or misleading;
- 408 • Be indelibly printed on the label/labeling of the tobacco product on the side that is most
409 likely to be viewed by a consumer (if the packaging is too small to accommodate a
410 legible warning, FDA recommends that these warnings be permanently affixed on the
411 product's carton or other outer container, wrapper, or a tag otherwise permanently affixed
412 to the tobacco product package);



- 413 • Include bold colorings and markings containing pictographs—that could be understood
- 414 by a child who cannot read—to discourage opening and ingesting the package contents;
- 415 • Provide a statement regarding nicotine being a dangerous substance and the potential for
- 416 nicotine poisoning;
- 417 • Describe the mode or process of possible accidental exposure;
- 418 • Include a specific statement about keeping e-liquids out of the reach of children and pets;
- 419 and
- 420 • Include instructions to seek medical help if accidental contact occurs.

421
422 The text below is an example of a textual nicotine exposure warning which should be modified
423 as appropriate for your product. Although this example is not accompanied by pictographs, your
424 warnings should also include pictographs as recommended above.

425
426 **WARNING:** Contains nicotine, which can be poisonous. Avoid contact with skin and
427 eyes. Do not drink. Keep out of reach of children and pets. In case of accidental contact,
428 seek medical help.

429
430 c. Warning statement regarding the addictiveness of nicotine

431
432 In accordance with 21 CFR 1143.3(a)(1), it is unlawful for any person to manufacture, package,
433 sell, offer to sell, distribute, or import for sale or distribution within the United States any
434 cigarette tobacco, roll-your-own tobacco, or covered tobacco product other than cigars, unless
435 the **package** label bears the following warning statement: “WARNING: This product contains
436 nicotine. Nicotine is an addictive chemical.” A covered tobacco product is any tobacco product
437 deemed pursuant to 21 CFR §1100.1 to be subject to the FD&C Act, but excludes any
438 component or part of a tobacco product that is not made or derived from tobacco. Therefore, any
439 ENDS product that contains nicotine or tobacco is a covered tobacco product and must comply
440 with the requirement that the package label bear a warning statement regarding the addictiveness
441 of nicotine. The specimens of labeling included in a PMTA under section 910(b)(1)(F) of the
442 FD&C Act must include package labels with the required warning statement on the addictiveness
443 of nicotine.

444
445 21 CFR 1143.3(d) requires that if a tobacco product is too small or otherwise unable to
446 accommodate a label with sufficient space to bear the warning statement regarding the
447 addictiveness of nicotine, the warning must appear on the carton or other outer container or
448 wrapper if the carton, outer container, or wrapper has sufficient space to bear such information,
449 or appears on a tag otherwise permanently affixed to the tobacco product package.⁸ For new
450 tobacco products too small or otherwise unable to accommodate the warning on the label, you
451 must submit specimens of the outer container or wrapper or the tag otherwise permanently
452 affixed to the tobacco product package and explain how the outer container, wrapping, or tag
453 will be attached to the tobacco product.

⁸ See 21 CFR part 1143 for the complete list of requirements for the required warning statement regarding the addictiveness of nicotine.



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d. Child-resistant packaging

Given the health risks and hazards associated with exposure to e-liquids (including oral, dermal, and ocular dangers), especially to infants and children, FDA recommends that manufacturers provide sufficient information describing the kind of child-resistant packaging their ENDS product will be sold in to support a finding that the marketing of the product is appropriate for the protection of the public health. The description should also include information regarding the tamper-resistant and tamper-evident⁹ properties of the packaging. An example of child-resistant packaging that would help show the product is appropriate for the protection of the public health is, depending on the circumstances, packaging that is significantly difficult for children 5 years of age and under to open, use, or obtain a toxic, potentially addicting, or otherwise harmful amount of the tobacco product or any of its constituents within a reasonable time and that is not unreasonably difficult for a majority of adults to use properly.

V. HOW TO SUBMIT A PMTA

FDA strongly encourages you to submit your PMTA in an electronic format to facilitate efficiency and timeliness of data submission and processing. You can securely submit your PMTA via the FDA Electronic Submissions Gateway (ESG). Refer to the ESG website instructions for setting up a WebTrader account online at

[Redacted] Information about the eSubmitter tool can be found online at [Redacted]

Additionally, to help prepare for a potential referral of your PMTA to the TPSAC, FDA recommends that you identify information that you believe to be a trade secret or confidential, commercial information that is contained in your PMTA. You can identify this information by submitting two separate and complete versions of the PMTA: one unredacted version and one marked-for-redaction version. The marked-for-redaction version should denote the content that is the subject of a proposed redaction at the place where the text is located in the document in a manner that allows the text to remain legible, such as placing a box around the content. You should also submit an index that lists the location of each proposed redaction in the PMTA by page number and you should explain, in detail, why you believe, each proposed redaction qualifies as a trade secret or confidential, commercial information that is not available for disclosure under 21 CFR 21.61.

You may withdraw your PMTA at any time until FDA issues an order granting or denying a marketing order. Please notify FDA in writing if you wish to withdraw your PMTA. This notification should be clearly labeled as a PMTA withdrawal and submitted through the electronic system or sent to the following address:

⁹ Tamper-evident packaging is designed to provide visible evidence to consumers that tampering has occurred, such as a torn label or a tear in a blister pack.



496 Food and Drug Administration
497 Center for Tobacco Products



503 **VI. CONTENT OF A PREMARKET TOBACCO PRODUCT APPLICATION FOR**
504 **ENDS PRODUCTS**

505
506 Your PMTA must include all information that is required by section 910(b)(1) of the FD&C Act.
507 Under section 910(b)(1), the application must contain:

- 508
- 509 • Full reports of all information, published or known to, or which should reasonably be
510 known to, the applicant, concerning investigations which have been made to show the
511 health risks of such tobacco product and whether such tobacco product presents less risk
512 than other tobacco products;
- 513 • A full statement of the components, ingredients, additives, and properties, and of the
514 principle or principles of operation, of such tobacco product;
- 515 • A full description of the methods used in, and the facilities and controls used for, the
516 manufacture, processing, and, when relevant, packing and installation of, such tobacco
517 product;
- 518 • An identifying reference to any tobacco product standard under section 907 that would be
519 applicable to any aspect of such tobacco product, and either adequate information to
520 show that such aspect of such tobacco product fully meets such tobacco product standard
521 or adequate information to justify any deviation from such standard;
- 522 • Such samples of such tobacco product and of components thereof as the Secretary may
523 reasonably require;
- 524 • Specimens of the labeling proposed to be used for such tobacco product; and
- 525 • Such other information relevant to the subject matter of the application as the Secretary
526 may require.

527
528 Also, section 910(c)(5) requires FDA to base its determination to issue or not issue a marketing
529 order on well-controlled investigations or other valid scientific evidence which is sufficient to
530 evaluate the tobacco product.

531
532 This section discusses FDA's general recommendations for PMTA content, including the
533 mandatory requirements discussed in section 910, other recommendations, and an explanation of
534 FDA's current thinking on well-controlled investigations and other valid scientific information.
535 FDA recommends that you organize your PMTA content in the following order to aid in the
536 review of your PMTA. See sections VII through IX of this guidance document for additional
537 recommendations for PMTA content for certain types of ENDS products.

538
539 You may submit a single premarket submission for multiple products and a single, combined
540 cover letter and table of contents across all products; however, when FDA receives a premarket

[REDACTED]

541 submission that covers multiple, distinct new tobacco products, we intend to consider
542 information on each product as a separate, individual PMTA. Therefore, it is important that you
543 clearly identify and delineate what content pertains to each distinct product and show that you
544 have satisfied the requirements of section 910(b)(1) for each product. For example, FDA
545 considers each ENDS product with differing flavor variants and nicotine strengths to be a
546 different product.

547
548 FDA recommends that your PMTA be well organized, numbered using continuous pagination,
549 legible, and written in the English language. For any foreign language documents, you should
550 also provide the original foreign language document, the English translations, and certification
551 that the translation into English is accurate.

552
553 To facilitate review, each PMTA should:

- 554
- 555 • Be static, that is, the pages should not reformat, renumber, or re-date each time the
- 556 document is accessed;
- 557 • Enable the user to print each document page by page, as it would have been provided in
- 558 paper, maintaining fonts, special orientations, table formats, and page numbers; and
- 559 • Allow the user to copy text, images, and data electronically into other common software
- 560 formats.

561
562 You can find examples of acceptable file formats online at
563 [REDACTED]
564 [REDACTED]
565 [REDACTED]

566 **A. General Information**

567
568 FDA recommends that you include a cover letter that contains basic information identifying
569 yourself as the applicant and the specific product(s) for which you are seeking a marketing order.
570 This cover letter should prominently identify the submission with “Premarket Tobacco Product
571 Application (PMTA) – [Name of New Tobacco Product]” and include information such as:

- 572
- 573 • The name and address of your company;
- 574 • Your authorized U.S. agent or representative’s name, title, address, phone number, email
- 575 address, and fax number;
- 576 • Basic information identifying the new product, including the unique identification
- 577 information described in section VI.C;
- 578 • Identifying information regarding prior submissions for the new product, such as
- 579 substantial equivalence reports or previous PMTAs;
- 580 • Dates and purpose of any prior meetings with FDA regarding the new tobacco product;
- 581 • A brief statement regarding how the PMTA satisfies the content requirements of section
- 582 910(b)(1) of the FD&C Act, such as a table specifying which PMTA sections satisfy each
- 583 statutory requirement; and
- 584 • A list identifying all enclosures and labeling being submitted with the PMTA.
- 585



586 **B. Table of Contents**

587
588 FDA recommends that you include a comprehensive table of contents that specifies the section
589 and page number for each item included in the PMTA with hyperlinks to relevant pages in the
590 application. Your PMTA and any amendments also should contain a comprehensive index (i.e., a
591 list of files and metadata).

592
593 **C. Descriptive Information**

594
595 FDA recommends that you provide information describing the major aspects of the new tobacco
596 product, such as the following items:

- 597
598
- A unique identification of the new tobacco product;
 - A concise but complete description of the new tobacco product;
 - An identifying reference to any tobacco product standard under section 907 of the FD&C Act (21 U.S.C. 387g) that would be applicable to your new tobacco product and either information that shows your new tobacco product meets the tobacco product standard or adequate information justifying any deviation from such standard, as required in section 910(b)(1)(D);
 - An overview of the product's formulation and design, as part of the full statement of properties required by section 910(b)(1)(B);
 - The name and description of any characterizing flavor the product contains, if applicable;
 - The nicotine strength;
 - The conditions for using the product or instructions for use, as part of the full statement of the principle or principles of operation required by 910(b)(1)(B), and, if known, problems with use in previous or similar versions of the new product; and
 - If applicable, any restrictions on the sales and distribution of the new tobacco product that you propose to be included as part of a marketing order under section 910(c)(1)(B) to help support a showing that the marketing of the product is appropriate for the protection of the public health.
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616
617 FDA recommends that the unique identification of the product include:

- 618
- For E-liquids:
 - Product name
 - Category: ENDS
 - Subcategory: E-Liquid
 - Package type
 - Package quantity (mL)
 - Characterizing flavor
 - Nicotine content (%)
 - For Closed Aerosolizing Apparatus or a Prefilled Open Aerosolizing Apparatus:
 - Product name
 - Category: ENDS
- 619
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- 630 ○ Subcategory: Closed Aerosolizing Apparatus or Prefilled Open Aerosolizing
- 631 Apparatus
- 632 ○ Package type
- 633 ○ Characterizing flavor
- 634 ○ Nicotine content (%)
- 635 ○ E-liquid capacity (mL)
- 636 ○ Coil resistance (Ohms)
- 637 ○ Battery capacity (mAh)
- 638 ● For Open Aerosolizing Apparatus (Without E-liquid and Including Components and Parts
- 639 of Open Aerosolizing Apparatus):
- 640 ○ Product name
- 641 ○ Category: ENDS
- 642 ○ Subcategory: Open Aerosolizing Apparatus
- 643 ○ Package type
- 644 ○ E-liquid capacity (mL)
- 645 ○ Coil resistance (Ohms)
- 646 ○ Battery capacity (mAh)
- 647 ● For ENDS Bundle¹⁰:
- 648 ○ Product name
- 649 ○ Category: ENDS
- 650 ○ Subcategory: ENDS Bundle
- 651 ○ Package type
- 652 ○ Package quantity (mL)
- 653 ○ Characterizing flavor
- 654 ○ Nicotine content (%)
- 655 ○ E-liquid capacity (mL)
- 656 ○ Coil resistance (Ohms)
- 657 ○ Battery capacity (mAh)

658 **D. Product Samples**

661 Section 910(b)(1)(E) of the FD&C Act requires that a PMTA application contain samples of the
662 new tobacco product and its components as FDA may reasonably require. FDA recommends that
663 applicants provide at least one sample of the new finished tobacco product that is the subject of
664 the PMTA. FDA may conduct its own testing and analysis of the new tobacco product and its
665 components and may request a reasonable number of additional samples for testing and analyses.
666 FDA will send the applicant a letter acknowledging the receipt of the PMTA that includes
667 information on how to submit the sample(s). Applicants should be ready to send a sample when
668 they submit their PMTAs, and we recommend submitting the sample no later than 7 calendar
669 days after the date of the acknowledgement letter. Samples should be submitted to the Southeast

¹⁰ An *ENDS Bundle* refers to an open aerosolizing apparatus or a component or part that is sold or distributed to consumers in the same package as separately contained e-liquids or prefilled with e-liquid.



670 Regional Laboratory. The address and how to identify the sample or samples will be specified in
671 the acknowledgement letter.

672
673 **E. Labeling**

674
675 As required by section 910(b)(1)(F) of the FD&C Act, your PMTA must include specimens of
676 all proposed labeling for your new tobacco product. The term *labeling* is defined in section
677 201(m) of the FD&C Act as “all labels and other written, printed, or graphic matter (1) upon any
678 article or any of its containers or wrappers, or (2) accompanying such article,” and includes
679 labels, inserts, onserts, instructions, and other accompanying information or materials (section
680 201(m) of the FD&C Act (21 U.S.C. 321(m)). The submitted specimens of proposed labeling for
681 all product panels should reflect the actual size and color for use with the new tobacco product as
682 part of your PMTA. All labeling you submit also should include any warning statements
683 appropriate for the product class where applicable, such as the required addiction and
684 recommended nicotine exposure warnings included in section IV.D.2 of this guidance, and
685 should comply with all other applicable labeling requirements under the FD&C Act.

686
687 FDA recommends that your product labeling include text or graphic elements (in addition to the
688 required warning statement regarding the addictiveness of nicotine and the suggested nicotine
689 exposure warning) to minimize risks associated with use of the product and text or graphic
690 elements to identify the product. Text or graphic elements to minimize risks should be directed at
691 both users and nonusers of the tobacco product and should include directions for use, storage,
692 and **recharging**, if applicable. For example, the text or graphic could help to show that risk of
693 battery failure would be minimized by recharging the product only with specified chargers or
694 that the product’s composition is stabilized by certain storage conditions. Identification elements
695 can include information on your label, such as the batch number, expiration date, and unique
696 identifier bar codes. FDA encourages applicants to use font types and sizes and organizational
697 formats (such as bulleted lists) that are legible and conspicuous, making it easy for consumers to
698 read and understand.

699
700 **F. Environmental Assessment**

701
702 Under 21 CFR 25.15, an applicant must include an environmental assessment prepared in
703 accordance with 21 CFR 25.40, unless the action qualifies for a categorical exclusion. More
704 information on environmental assessments can be found in 21 CFR 25.

705
706 **G. Summary of All Research Findings**

707
708 Your PMTA should contain a well-structured summary to provide FDA with an adequate
709 understanding of the data and information in the PMTA, including the quantitative aspects of the
710 data. FDA recommends that you include a section summarizing all research findings in your
711 PMTA, including a description of the operation of the new tobacco product, the health risks of
712 the product, the product’s effect on tobacco use behavior among current users, the product’s
713 effect on tobacco use initiation among nonusers, and the product’s effect on the population as a
714 whole. The discussion should include information such as:



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- A summary of the nonclinical and clinical studies, both favorable and unfavorable, relevant to your PMTA, including which specific product or products were studied, how those products are similar to the applicant’s product if used as a substitute or supplement for data for the product, the study findings, and if the findings concern health risks compared to other tobacco products, whether such product presents less risk than other tobacco products, if similar or not to the applicant’s tobacco product. If no relevant health information is available, we recommend that you state this in this section;
- The health risks of the new tobacco product for both users and nonusers compared to other tobacco products on the market (e.g., other ENDS, combusted tobacco products such as cigarettes) and the health risks compared to never using tobacco products;
- The chemical and physical identity and quantitative levels of the emission of aerosols under the range of operating conditions of the product;
- The likelihood, based on the research findings contained in your application, of consumers initiating or reinitiating tobacco use with the new tobacco product;
- The likelihood, based on the research findings contained in your application, that consumers will adopt the new tobacco product and then switch to other tobacco products that may present higher levels of risk;
- The likelihood, based on the research findings contained in your application, of consumers using the new tobacco product in conjunction with other tobacco products;
- The likelihood, based on the research findings contained in your application, of consumers switching to the product instead of ceasing tobacco product use or using an FDA-approved tobacco cessation product;
- Assessment of abuse liability;
- Assessment of user topography; and
- A discussion demonstrating how the data and information contained in your PMTA establish that the new tobacco product is appropriate for the protection of the public health.

FDA also recommends that you provide quantitative estimates of the effect that the new tobacco product may have on the health of the population as a whole. The estimates should integrate all of the information regarding the product and its potential effects on health, tobacco use behavior and tobacco use initiation to provide an overall assessment of the potential effect that the product’s marketing may have on overall tobacco-related morbidity and mortality.

H. Scientific Studies and Analyses

FDA recommends organizing the full reports, full statements, and full descriptions of all scientific studies and analyses referenced elsewhere in the PMTA into this section. For each study, you should indicate whether the product studied is identical to the new tobacco product, a different version of the new tobacco product (e.g., an earlier prototype), or another comparable product.

1. Product Analyses and Manufacturing



760 FDA recommends that this section contain the detailed technical information and analyses
761 concerning your new tobacco product and its manufacturing that is required by sections
762 910(b)(1)(B)-(C) of the FD&C Act.

763
764 Product analyses and testing should be conducted on the ENDS tobacco product subject to the
765 PMTA. The product sample submitted (as discussed in section VI.D of this guidance) should be
766 from one of the batches tested for purposes of this section if the sample is still within its shelf
767 life. Otherwise, the sample should be one with a shelf life current at the time of submission.
768 FDA recommends that, for each product analysis or testing that is included in this section of your
769 PMTA, you include full reports of all testing, including the following information, where
770 applicable:

- 771
- 772 • Source data (please note that the data sets should span a minimum of three different
773 batches with a minimum of 10 replicates per batch, with date and time sampling points);
 - 774 • Accreditation information for each testing laboratory;
 - 775 • Validation information and rationale for selecting each test method, including any
776 relevant voluntary testing standards; and
 - 777 • Complete descriptions of any aerosol-generating regimens used for analytical testing.

778
779 a. Components, ingredients, and additives

780
781 The chemistry of the product is a major indicator of the consumer's exposure to health risks.
782 Section 910(b)(1)(B) of the FD&C Act requires a full statement of the components, ingredients,
783 additives, and properties, and of the principle or principles of operation, of such tobacco product
784 as part of your PMTA. FDA interprets this requirement to mean that you should provide a
785 complete list of uniquely identified components, ingredients, and additives by quantity in the
786 new products, as well as the applicable specifications and a description of the intended function
787 for each. Components, ingredients, and additives include anything, other than accessories, that
788 may reasonably be expected to directly or indirectly become part of, or affect the characteristics
789 of, the finished new tobacco product (including, but not limited to, liquid reservoirs, solvents,
790 flavor additives, heating coils, batteries, and pH modifiers). FDA recommends listing
791 information regarding the product's container closure system. The container closure system
792 refers to the packaging components that contain and protect a tobacco product, even if they are
793 not in direct contact with the tobacco product, but are intended to provide protection to the
794 product as it moves through the distribution system. For example, for e-liquids, this would
795 include the container the liquid is in (e.g., a glass or plastic vial, a cartridge, etc.). The container
796 closure system can often affect or alter the performance, composition, constituents, or
797 characteristics of a tobacco product. For example, the container closure system can, intentionally
798 or unintentionally, leach ingredients from the packaging into the product. This list should also
799 specify the function(s) and grade or purity for each respective item. For guidance on uniquely
800 identifying components, ingredients, and additives and reporting their quantities, please refer to
801 FDA's guidance for industry, *Listing of Ingredients in Tobacco Products*.

802
803 FDA does not believe there is adequate scientific information or regulatory experience with
804 ENDS products to support using only information on earlier or other versions of the product or



805 similar products for descriptions of full product analysis as described in this section. If you feel
806 that literature reviews may be an appropriate means for satisfying the requirements of section
807 910(b)(1)(B), please explain clearly how an adequate comparison (e.g., bridging) can be made
808 between the products analyzed in the published material and the product that is the subject of
809 your PMTA.

810
811 FDA also recommends that you include a complete list of uniquely identified constituents,
812 including those listed below, as appropriate for your product, and other toxic chemicals
813 contained within the product or delivered by the product, such as a reaction product from
814 leaching or aging and aerosol generated through the heating of the product. Your constituent
815 testing should reflect the range of conditions under which consumers may use your product. For
816 example, an open aerosolizing apparatus (an aerosolizing apparatus that includes a refillable e-
817 liquid reservoir) should be tested with a wide range of available e-liquids; a closed aerosolizing
818 apparatus (an aerosolizing apparatus that includes an e-liquid reservoir that is not refillable)
819 should be tested with the e-liquids with which they are packaged and sold; components or parts
820 should be tested with the range of products with which they could be used; and e-liquids that can
821 be used with a wide range of aerosolizing apparatus should be tested with such a range of
822 aerosolizing apparatus with varying temperatures and voltage. FDA recommends that
823 measurements of constituents, including those listed below and other toxic chemicals, as
824 appropriate for your product, be evaluated under both nonintense use conditions and intense use
825 conditions to enable FDA to understand the likely range of delivery of emissions.

826
827 FDA recommends that you consider the following constituents¹¹ for analysis in e-liquids and
828 aerosols, as appropriate, for your product:

- 829
- 830 • Acetaldehyde
- 831 • Acetyl Propionyl (also known as 2,3-pentanedione)
- 832 • Acrolein
- 833 • Acrylonitrile
- 834 • 4-Aminobiphenyl
- 835 • 1-Aminonaphthalene
- 836 • 2-Aminonaphthalene
- 837 • Ammonia
- 838 • Anabasine
- 839 • Benzene
- 840 • Benzo[a]pyrene
- 841 • 1,3-Butadiene
- 842 • Cadmium
- 843 • Chromium
- 844 • Crotonaldehyde
- 845 • Diacetyl

¹¹ These constituents are constituents that, to FDA's current thinking, potentially could cause health hazards depending on the level, absorption, or interaction with other constituents.



- 846 • Diethylene glycol
- 847 • Ethylene glycol
- 848 • Formaldehyde
- 849 • Glycerol
- 850 • Isoprene
- 851 • Lead
- 852 • Menthol
- 853 • Nickel
- 854 • Nicotine, including total nicotine and unprotonated nicotine
- 855 • NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
- 856 • NNN (N-nitrosornicotine)
- 857 • Propylene glycol
- 858 • Toluene
- 859 • Other constituents, as appropriate

860
861 In addition to the constituents, FDA recommends that you report the pH of the e-liquids tested
862 and the resulting aerosol.

863
864 FDA also recommends that you submit information regarding any relevant voluntary standards
865 with which your product complies and why you believe the standard is relevant, as well as
866 testing to demonstrate conformance to such standards.

867
868 b. Properties

869
870 Properties of the product can influence a consumer's exposure to health risks. Section
871 910(b)(1)(B) of the FD&C Act requires that your PMTA include a full statement of the
872 properties of the new tobacco product. The "full statement of the properties" of the new tobacco
873 product should include a full narrative description of the tobacco product, including:

- 874
875 • A description of the product dimensions and the overall construction of the product
876 (using a diagram or schematic drawing that clearly depicts the finished product and its
877 components with dimensions, operating parameters, and materials);
- 878 • A description of all design features of the product, specifying the explicit range of or the
879 nominal values of the design features as well as the design tolerance, where appropriate;
- 880 • A quantitative description of the performance criteria;
- 881 • A description of product container closure system. The description should include
882 information on how the container closure system protects and preserves the product, such
883 as from damage during transport, environmental contaminants, leaching, and migration of
884 container closure system constituents into the products (FDA expects that this
885 documentation may be generated by the applicant, by the supplier of the material of
886 construction or the component, or by a laboratory under contract to either the applicant or
887 the manufacturer);
- 888 • A description of how the product's properties (e.g., product design parameters,
889 constituents) differ from similar, marketed tobacco products in the same category (i.e.,



890 comparator products). For example, if your PMTA is for an e-liquid, we recommend a
 891 comparison to other e-liquids with similar nicotine content, flavors, and other ingredients,
 892 used in the same manner and under similar conditions. You should describe both how
 893 your product may be similar and different from other products of the same category;

- 894 • Storage and stability information for the new tobacco product. This information should
 895 include the established shelf life of the product and changes in pH and constituents
 896 (including HPHCs and other toxic chemicals) over the lifespan of the product, such as the
 897 factors that determine the shelf life (e.g., volume of e-liquid, power supply, atomizer,
 898 coil); how stability is affected by the storage conditions, such as moisture and
 899 temperature; full reports of all stability testing; and how the product’s performance may
 900 significantly decline (e.g., decrease in aerosol flow rate or change in aerosol constituents)
 901 over the product’s lifetime; and
- 902 • Assessments of product design hazards that could be expected to result in illness or injury
 903 from normal use and foreseeable misuse of the product, including actions taken or future
 904 plans that show how a design hazard is reduced, mitigated, or eliminated. For example,
 905 you could assess whether the consumer could tamper with the heating element and how
 906 the manufacturer has responded to such an assessment so the product is not misused.

907
 908 c. Principles of operation

909
 910 Consumers may be able to alter an ENDS product’s effect by changing the product design, the
 911 way the product is used, or adding or subtracting other ingredients. Section 910(b)(1)(B) of the
 912 FD&C Act requires you to submit as part of your PMTA “a full statement of the . . . principle or
 913 principles of operation” of the new tobacco product. FDA interprets a full statement of principle
 914 or principles of operation to include a full narrative description of the way in which a consumer
 915 will use the new tobacco product, including a description of how a consumer operates the
 916 product, how the manufacturer reasonably believes a consumer could change the product
 917 characteristics, adjust the performance, or add or subtract ingredients. This description also
 918 should include the other types of ENDS products with which your product can be used.

919
 920 d. Manufacturing

921
 922 The manufacturing descriptions show how the product is made to conform with the product
 923 information provided in the PMTA. As required by section 910(b)(1)(C) of the FD&C Act, you
 924 must provide a full description of the methods used in, and the facilities and controls used for,
 925 the manufacture, processing, and, where relevant, packing and installation of the new tobacco
 926 product, including e-liquids and aerosolizing apparatus.¹²

927
¹² The requirement to provide a full description of methods of manufacturing and processing is separate and distinct from good manufacturing practice requirements, the latter of which will be the subject of regulations under section 906(e) of the FD&C Act (21 U.S.C. 387f(e)). FDA will issue regulations under section 906(e) that will contain the requirements for demonstrating good manufacturing practices. At that time, each PMTA will also be expected to demonstrate that the methods, facilities, or controls used conform to these regulations (section 910(c)(2)(B)).



928 FDA recommends that you provide a listing of all manufacturing, packaging, and control sites
929 for the product, including the facility names and addresses, and a contact name and telephone
930 number for each facility. Moreover, we recommend that you provide a narrative description,
931 accompanied by a list and summary of all standard operating procedures (SOPs) and examples of
932 relevant forms and records, for the following categories of information:

- 933
- 934 • Manufacturing and production activities, including a description of facilities and all
935 production steps;
- 936 • Managerial oversight and employee training;
- 937 • Manufacturing processes and controls for product design, including a hazard analysis that
938 details the correlation of the product design attributes with public health risk, and any
939 mitigations implemented;
- 940 • Activities related to identifying and monitoring suppliers and the products supplied
941 (including, for example, purchase controls and materials acceptance activities);
- 942 • Validation and verification activities used to ensure that the new tobacco product matches
943 specifications, including any voluntary standards with which your product complies;
- 944 • Testing procedures conducted before the new tobacco product is released for sale and
945 distribution in the U.S., including information such as the concentration of the standard
946 solution as well as a description of acceptance activities with protocol and acceptance
947 criteria. If the product is manufactured without a solution, you should describe its
948 performance characteristics (e.g., particle size, heating temperature); and
- 949 • Handling of complaints, nonconforming products and processes, and corrective and
950 preventive actions.

951

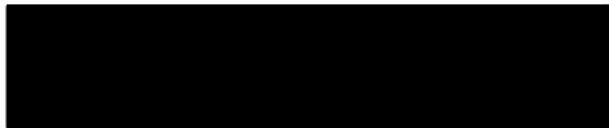
952 FDA may request that you submit copies of selected SOPs if needed to enable FDA to more fully
953 understand the methods used in, and the facilities and controls used for, the manufacturing and
954 processing of the new tobacco product.

955

956 *2. Nonclinical and Human Subject Studies*

957

958 Section 910(b)(1)(A) of the FD&C Act requires that a PMTA contain “full reports of all
959 information, published or known to, or which should reasonably be known to, the applicant,
960 concerning investigations which have been made to show the health risks of such tobacco
961 product and whether such tobacco product presents less risk than other tobacco products.” FDA
962 interprets the information required under this provision to include not only investigations that
963 support the PMTA, but also any investigations that do not support, or are adverse to, the PMTA.
964 Information on both nonclinical and clinical investigations should be provided, including, but not
965 limited to, any studies assessing constituents of tobacco, tobacco smoke, or aerosol, toxicology,
966 consumer exposure, and consumer use profiles. Furthermore, information on investigations
967 concerning products with novel components, ingredients, additives, or design features that are
968 similar or related to those of the new tobacco product and investigations concerning products that
969 share novel components, ingredients, additives, or design features with the new tobacco product
970 should also be provided so that FDA may adequately assess the product’s health risks. To the
971 extent the information is available, you should indicate the source of funding for all studies and
972 provide a statement regarding any potential financial conflicts of interest.



973
974 FDA interprets “full reports of all information, published or known to, or which should
975 reasonably be known to, the applicant” to include all information from investigations conducted
976 both within and outside the United States.¹³ While all clinical investigations (both within and
977 outside the United States) submitted with your PMTA should be conducted to ensure that the
978 rights, safety, and welfare of human subjects have been protected, you must (under section
979 910(b)(1)(A) of the FD&C Act) submit full reports of all information concerning relevant
980 clinical investigations even if the study did not protect the rights, safety, and welfare of human
981 subjects. One way to ensure that the rights, safety, and welfare of human subjects are protected is
982 to ensure that that clinical studies conducted or included in a PMTA are done so in accordance
983 with ethical principles acceptable to the international community (e.g., ICH E6 Good Clinical
984 Practice standards).¹⁴ Special attention should be paid to trials that may include vulnerable
985 subjects.¹⁵

986
987 Section 910(g) of the FD&C Act (21 U.S.C 387j(g)) gives FDA the authority to issue regulations
988 to exempt tobacco products intended for investigational use from the requirements of Chapter IX
989 of the FD&C Act, including premarket submission requirements. To date, FDA has not issued
990 such regulations, and consequently investigational tobacco products are not exempt from FD&C
991 Act requirements, including premarket submission requirements. Until regulations governing the
992 use of investigational tobacco products are issued and finalized, FDA intends to evaluate specific
993 uses of investigational tobacco products according to potential public health concerns or other
994 impacts on public health.¹⁶ Applicants who would like to study their new tobacco products to
995 support a premarket submission should contact the Office of Science at the Center for Tobacco
996 Products to discuss submission of a study protocol and/or study endpoints.¹⁷
997

¹³ As discussed in section X of this guidance, well-controlled investigations conducted outside the United States may be submitted to FDA in support of a PMTA. If you submit a study or studies conducted outside the United States in support of your PMTA, you should provide an explanation of how the rights, safety, and welfare of human subjects were protected or, if you do not know and are unable to provide this information, you should explain why (e.g., because you were not the sponsor of those studies).

¹⁴ For information on how good clinical practice standards have been used in other contexts, see FDA’s guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*, available on the Internet at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073122.pdf>.

¹⁵ For information on considerations on clinical trials with vulnerable subjects, see 21 CFR 56.

¹⁶ When finalized, the guidance for industry and investigators *Use of Investigational Tobacco Products* will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Tobacco Product Guidance page at <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm>.

¹⁷ Information about how to request meetings with CTP can be found in FDA’s guidance for industry and investigators *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, available on the Internet at <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM305282.pdf>.



998 For published studies concerning investigations that have been conducted to show the health
999 risks of your new tobacco product, you should provide a bibliography of the studies and a full
1000 article for each study. You should also provide an explanation of the scope of the literature
1001 review you conducted to discover the relevant published studies, including how you identified,
1002 collected, and reviewed the studies. However, for studies that you conducted or that were
1003 conducted on your behalf, you should submit full study reports and data.

1004
1005 Your PMTA should include a summary of the results and methods of each study you submit.
1006 Information about studies' methodology and procedures help FDA assess the strength of the
1007 study. The summary should include, where available or reasonably obtainable:

- 1008
- 1009 • A description of the study objective;
- 1010 • A description of the study design (or hypothesis tested);
- 1011 • A description of any statistical analysis plan, including how data were collected and
1012 analyzed; and
- 1013 • A brief description of the findings and conclusions (positive, negative, or inconclusive).
- 1014

1015 In addition, for each study regarding the health risks of the new tobacco product, you should
1016 include, to the extent available or reasonably obtainable:

- 1017
- 1018 • Documentation of all actions taken to ensure the reliability of the study, such as
1019 appropriate good laboratory practices found in 21 CFR part 58, as applicable;
- 1020 • Copies of all investigator instructions produced in addition to the protocol, if any;
- 1021 • The statistical analysis plan, including a detailed description of the statistical analyses
1022 employed (i.e., all variables, confounders, and subgroup analyses and any amendments);
- 1023 • A list of the sites where a study was conducted, including contact information and
1024 physical address(es);
- 1025 • Source data. To facilitate our review, we request data in SAS-transport file in XPT
1026 format, created by a procedure that allows the files to be readily read by the JMP
1027 software. We also request that you provide data definition files that include the names of
1028 the variables, codes, and formats used in each dataset, and copies of SAS programs and
1029 necessary macro programs used to create derived datasets and the results reported in the
1030 study reports;
- 1031 • The location of all source data. If the site has not maintained all of the source data,
1032 indicate where the data are located;
- 1033 • The format of the records and data (e.g., electronic, hard copy);
- 1034 • A copy of any protocols and amendments that were used in the study;
- 1035 • A list of all contractors who participated in the study, the role of each contractor, and the
1036 initiation and termination dates of the participation of each contractor; and
- 1037 • A signed full report of the findings.
- 1038

1039 In addition, for clinical studies, you should include, to the extent available or reasonably
1040 obtainable:

1041



- 1042 • Documentation of all actions taken to ensure the reliability of the study and the protection
- 1043 of human subjects (e.g., documentation of study oversight by an Investigational Review
- 1044 Board duly constituted and operating under 21 CFR part 56; documentation of informed
- 1045 consent procedures, such as appropriate procedures found in 21 CFR part 50; and
- 1046 documentation of appropriate good laboratory practices, such as those found in 21 CFR
- 1047 part 58);
- 1048 • All versions of questionnaires used;
- 1049 • All versions of case report forms used; and
- 1050 • All versions of informed consent forms.

1051
1052 Please note that individual subject case report forms and informed consent forms do not need to
1053 be submitted in the PMTA, but may be requested by FDA for further review if necessary to
1054 determine that marketing of the product is appropriate for the protection of the public health.

1055
1056 a. Nonclinical health risk information

1057
1058 Although nonclinical studies alone are generally not sufficient to support a determination that
1059 marketing of the product is appropriate for the protection of the public health (PMTAs would
1060 generally need clinical data), information from these nonclinical studies provides insight into the
1061 mechanisms of disease incidence caused by a tobacco product and, more generally, provides
1062 context for the data obtained from human studies regarding health risks, including addiction.
1063 Information on how manufacturers may want to address human study (clinical) information with
1064 new studies or existing studies, data, and literature is discussed in this guidance later in this
1065 section and in Section X.

1066
1067 Nonclinical health risk information should provide a thorough toxicological and pharmacological
1068 evaluation of each of the ingredients, mixture of ingredients, and aerosols produced by the new
1069 tobacco product. FDA recommends that a full assessment of the toxicological profile associated
1070 with the new tobacco product include, if available:

- 1071
- 1072 • Toxicology data from the literature (i.e., all relevant publications);
- 1073 • Analysis of constituents and other toxicants under both intense and non-intense use
- 1074 conditions as described in Section VI.H.1.a;
- 1075 • In vitro toxicology studies (e.g., genotoxicity studies, cytotoxicity studies);
- 1076 • In vivo toxicology studies (to address unique toxicology issues that cannot be addressed
- 1077 by alternative approaches); and
- 1078 • Computational modeling.

1079
1080 A thorough literature review, including publically available toxicology databases, can provide
1081 valuable information on the toxicity of the ingredients in the e-liquid and aerosol by the expected
1082 route of administration and level of exposure. This section should include:

- 1083
- 1084 • A description of the search methodology;



- 1085 • All publications related to the toxicological evaluation of each of the ingredients
- 1086 (nicotine, glycerol, propylene glycol, flavors, metals, and others) and the mixture of the
- 1087 ingredients in the e-liquid and aerosol produced from the ENDS;
- 1088 • Particular attention to information regarding oral, inhalation, dermal, and ocular routes of
- 1089 exposure;
- 1090 • Extractable leachable information from the aerosolizing apparatus;
- 1091 • Toxicological endpoints such as cytotoxicity, genotoxicity, and respiratory, cardiac,
- 1092 reproductive, and developmental toxicity;
- 1093 • Hazard identification studies;
- 1094 • Exposure kinetics, metabolism, and deposition and elimination profile of the ingredients,
- 1095 when available;
- 1096 • A conclusion as to whether there is a toxicological concern with respect to the
- 1097 ingredients, constituents, flavors, humectants, and mixtures of humectants (glycerin,
- 1098 propylene glycol, and other ingredients) that will be delivered in the aerosol from the use
- 1099 of the new tobacco product; and
- 1100 • Information on physicochemical changes of the mixture of ingredients in your product due
- 1101 to temperature, wattage, and/or voltage changes, if available.

1102
1103 Information generated from the new tobacco product itself also provides valuable insight into the
1104 toxicity profile of the product. This information may include the analyses of constituents and
1105 other toxic compounds in the ENDS aerosol. It can also include in vitro studies, in vivo studies,
1106 or both with the ENDS product itself. These studies might be conducted if an applicant is unable
1107 to acquire publically available toxicology information for specific aerosol ingredients. For any
1108 toxicity studies conducted prospectively, the following points should be considered:

- 1109
1110 • Studies should be based on the potential human exposure of the product. At a minimum,
- 1111 exposures that mimic the highest consumer use scenario and one lower exposure level
- 1112 should be evaluated in the toxicology studies. Analysis of constituents and toxicant levels
- 1113 at the exposures tested should be included.
- 1114 • If the consumer can change the voltage and/or temperature of the heating element, we
- 1115 recommend that you provide any available data on the subsequent changes in the aerosol
- 1116 ingredients. Please also include any toxicity information relevant to these changes.
- 1117 • We recommend that you provide aerosolization properties of each of the ingredients (e.g.,
- 1118 constituents, humectants, metals, flavors included), particle size of these ingredients in
- 1119 the product, and deposition of these particles through inhalation. We also recommend that
- 1120 you discuss how these properties could affect the product's toxicity profile.
- 1121 • In vitro assays can be used to evaluate the genotoxic potential of the ENDS in
- 1122 comparison to other tobacco products. We suggest using the ICH S2(R1) guidance and
- 1123 Organization for Economic Cooperation and Development protocols as a guide for
- 1124 genotoxicity assessment. We also recommend that you conduct these assays with
- 1125 multiple concentrations of your final product for validating your results. For appropriate
- 1126 hazard identification comparison, you should include the comparator products (i.e.,
- 1127 products in the same category) in your in vitro assay.
- 1128



1129 FDA supports reducing the reliance on animal testing where adequate and scientifically valid
1130 non-animal alternatives can be substituted. FDA encourages sponsors to meet with CTP early in
1131 the development process to discuss what, if any, animal testing is appropriate and the suitability
1132 and acceptability of non-animal tests for their particular new tobacco product. In all cases where
1133 animal testing is used, FDA advocates that research and testing derive the maximum amount of
1134 useful scientific information from the minimum number of animals, employ the most humane
1135 methods available within the limits of scientific capability, and comply with applicable laws,
1136 regulations, and policies governing animal testing.

1137
1138 In addition to the available literature and any data generated on the specific product, a strong
1139 scientific justification for the potential daily exposure levels of users to an aerosol from an
1140 ENDS product should be included. This information is important to enable FDA to conduct a
1141 thorough evaluation of the toxicity potential of the new tobacco product. The aerosol exposure
1142 levels should reflect the best available science on how exposures will occur in consumers based
1143 on the intended use of the ENDS product. In addition, we recommend that you provide the
1144 scientific rationale for the selection of the daily exposure to any other tobacco products used as
1145 comparators. The assumptions used to determine the exposure levels from the ENDS product
1146 (including aerosol) versus other tobacco products should be clearly articulated. Your nonclinical
1147 information section should then use this exposure information to inform the comparisons of all
1148 ingredients (including constituents, flavors, metals, and other e-liquid additives such as
1149 propylene glycol and glycerol) between the ENDS product and the product used as a comparator
1150 in your PMTA submission.

1151
1152 FDA recommends that you identify the key features in the new tobacco product that affect the
1153 levels of toxicants contained in the aerosol and provide evidence that key parameters in the
1154 product are stable with batch-to-batch testing.

1155
1156 In the absence of toxicological data for a particular toxicant of concern, we recommend that you
1157 consider computational modeling using surrogate chemical structures. If computational modeling
1158 is used, detailed modeling information should be provided including all source data, equations,
1159 assumptions, parameters, outputs, and references, as well a validation of the model. When you
1160 are using the model to evaluate the risk of a new tobacco product, we recommend that you utilize
1161 assumptions, equations, and parameters appropriate to the characteristics of the product and
1162 appropriate for the selected population of product users. If you plan to conduct any
1163 computational modeling, we suggest that you meet with CTP to specifically address this issue.
1164 Finally, we recommend that you provide an integrated summary discussing how the new tobacco
1165 product would be appropriate for the protection of the public health from a toxicology
1166 perspective relative to any similar comparator tobacco products (when those products are used in
1167 the same manner, under similar conditions, and for the same duration and frequency).

1168
1169 b. Human health impact information

1170
1171 Your PMTA should provide data that adequately characterizes the likely impact of the new
1172 tobacco product on the health of both users and nonusers of tobacco products in order to support
1173 that marketing the new tobacco product would be appropriate for the protection of the public



1174 health. To evaluate the acute and chronic health effects associated with the product, FDA
1175 recommends including studies, other scientific evidence, or both, that identify biomarkers of
1176 exposure, biomarkers of harm, and health outcome measurements or endpoints. For example,
1177 biomarkers of toxicant exposure may include compounds such as cotinine, NNAL, and NNN.
1178 Considerations in addressing the human health impact of a new tobacco product may include, but
1179 are not limited to:

- 1180
- 1181 • Tobacco users who may switch from other tobacco products to the new tobacco product;
- 1182 • Tobacco users and nonusers who, after adopting the new tobacco product, may switch to
1183 or switch back to other tobacco products that may present higher levels of individual
1184 health risk;
- 1185 • Tobacco users who may opt to use the new tobacco product rather than cease tobacco use
1186 altogether;
- 1187 • Tobacco users who may opt to use the new tobacco product rather than an FDA-approved
1188 tobacco cessation medication;
- 1189 • Tobacco users who may use the new tobacco product in conjunction with other tobacco
1190 products;
- 1191 • Nonusers, such as youth, never users, and former users, who may initiate or relapse
1192 tobacco use with the new tobacco product;
- 1193 • The health effects in users of the new tobacco product; and
- 1194 • Nonusers who experience adverse health effects from the new tobacco product.
- 1195

1196 Addressing these considerations in a full assessment of the health effects associated with your
1197 ENDS product may include evaluation of the following:

1198

1199 i. Consumer perceptions

1200

1201 Consumer perception evaluations should address how consumers perceive product risk and
1202 include consideration of packaging and labeling. Examples of information that may be
1203 considered in this analysis include published reports and data on consumer perceptions of the
1204 new tobacco product and its packaging, and data you collect on consumer perceptions of the
1205 harms of the new tobacco product and of its proposed labeling or advertising. If you are
1206 collecting data on consumer perceptions, we recommend evaluating perceptions of product risk,
1207 both absolute and in comparison to other categories of tobacco products, as well as to quitting all
1208 tobacco use. This evaluation should include the use intentions among current ENDS users,
1209 nonusers, and other tobacco product users, as well as reasons for use (e.g., complete substitution,
1210 use in environments where smoking is not allowed, fun and enjoyment).

1211

1212 ii. Likelihood of initiation and cessation by both users and nonusers of
1213 tobacco products

1214

1215 Evaluations of the likelihood of initiation among never-users and former users of tobacco
1216 products and cessation among current tobacco users should cover a range of tobacco use
1217 behaviors related to your new tobacco product. Examples of information that FDA recommends
1218 considering in these evaluations include:



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- Published literature or sponsor-initiated studies evaluating the effects of the ENDS on users and nonusers, including effects on initiation, switching behavior, cessation, and dual use. Published literature or studies should be of the same or similar ENDS product. Where the ENDS product studied is similar to the new tobacco product, the applicant will be responsible for providing justification for why making such a comparison is appropriate; and
- Scientific information on the likelihood of product use by youth, young adults, pregnant women, and other vulnerable populations.

Although randomized clinical trials could address cessation behavior of users of tobacco products, the likely impact of the tobacco product on cessation behavior instead could be evaluated through other types of studies, such as observational studies (perception, actual use, or both).¹⁸

iii. Product use patterns

Evaluation of product use patterns should consider the topography of how individual users consume the product (e.g., the number of puffs, puff duration, puff intensity, duration of use), the frequency with which consumers use the product, the trends by which users consume the product over time, the switching and cessation rates for users of the product, and the potential for consumers to use the product in conjunction with other tobacco products (e.g., dual use). Descriptive data on product use, including use in conjunction with other tobacco products, should be broken down by demographic factors, such as age group (including youth and young adults), sex, race, ethnicity, and education; and by geographic regions (e.g., U.S. census regions).

FDA also recommends sharing your marketing plan for FDA to better understand the potential consumer demographic. In addition, and, if the product is currently marketed,¹⁹ FDA recommends sharing sales data by population demographics and tobacco use status. If sales data are available, it should be analyzed in 4-week or monthly intervals, if data are available, and include:

- The Universal Product Code that corresponds to the product(s) identified in the PMTA;
- Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops) promotional discounts (e.g. buy-one-get-one free or percentage discount);

¹⁸ FDA recognizes that some clinical investigations examining cessation may require an investigational new drug (IND) application. FDA encourages applicants to contact FDA with questions about whether the IND requirements apply to a particular clinical investigation.

¹⁹ FDA recognizes that some products covered by this guidance were on the market before FDA deemed all tobacco products subject to the FD&C Act and would expect that some would continue to be on the market during the final deeming rule's compliance period. These currently marketed products should provide data on current US sales.



- 1256 • Demographic characteristics of product(s) purchasers, such as age, gender, and tobacco
1257 use status; and
- 1258 • Information on top selling brands as a comparison for all recommended information, if
1259 available, so FDA can assess the market for the PMTA product to better estimate the
1260 potential impact on public health.

1261
1262 iv. Labeling comprehension, self-selection, and actual use
1263

1264 FDA recommends that you include studies demonstrating that users and nonusers understand the
1265 product's labeling and instructions for use, and use the product according to its labeled
1266 instructions. FDA also recommends that you provide a description of how the product is actually
1267 used by the consumer, including both use as intended and use as not intended.
1268

1269 v. Human factors
1270

1271 Analyses to evaluate the impact of human factors may be helpful to identify risks associated with
1272 "real world" use of a new tobacco product and demonstrate that potential risks associated with
1273 use for both users and nonusers have been mitigated.
1274

1275 Human factors considerations and analyses should include studies that identify:
1276

- 1277 • Normal use and foreseeable misuse conditions;
- 1278 • Product users and nonusers;
- 1279 • Use environment, such as home, community settings, and mobile environments (e.g.,
1280 cars, planes, other public forms of transportation);
- 1281 • Use-related hazards and estimated use error risk (including misuse);
- 1282 • Risk controls to ensure that harms and unintended consequences are minimized; and
- 1283 • Adverse experiences.

1284
1285 vi. Abuse liability
1286

1287 Abuse liability evaluations, including pharmacokinetic evaluations, should consider the
1288 addictiveness and abuse and misuse potential of the new product and the exposure to nicotine
1289 during product use. These evaluations should consider:
1290

- 1291 • Published reports and data describing the abuse potential of the e-liquid and aerosolizing
1292 apparatus independently as well as when the products are used together, as it relates to
1293 other tobacco products; and
- 1294 • Published reports and pharmacokinetic data (including published reports) examining the
1295 exposure to nicotine during use.

1296
1297 vii. Biomarkers of harm and biomarkers of exposure
1298

1299 Biomarkers of harm and biomarkers of exposure may include published reports or data on
1300 biomarkers of harm, biomarkers of exposure, and/or other intermediate health outcomes to users



1301 and nonusers. For example, biomarkers of toxicant exposure may include compounds such as
1302 cotinine, NNAL, and NNN.

1303
1304 viii. Health outcomes

1305
1306 Data to support the impact of the new tobacco product on the health of users and nonusers may
1307 include health effects related to specific constituents that have been identified in the aerosol
1308 delivered to the user. These constituents will vary depending on the product and may include
1309 glycerin, propylene glycol, nicotine, flavorings, and metals. These data should include health
1310 effects of aerosol exposures, including changes in physiological measurements, such as heart rate
1311 and blood pressure; changes in lung, cardiac, and metabolic function; adverse experiences, such
1312 as throat irritation and cough; and changes in laboratory values, such as mediators of
1313 inflammation and complete blood count indices.

1314
1315 FDA recommends that you conduct studies to ensure, to the extent possible, that the study
1316 findings are generalizable to the population of U.S. users and nonusers of your new tobacco
1317 product. If you are relying on published reports to support your PMTA, you should justify why
1318 the data from those reports can be bridged to your product and are appropriate for determining
1319 the impact of the new tobacco product on the U.S. population.

1320
1321 **VII. ADDITIONAL RECOMMENDATIONS FOR PREMARKET TOBACCO**
1322 **PRODUCT APPLICATIONS FOR E-LIQUID PRODUCTS**

1323
1324 Because e-liquids have different properties and characteristics than aerosolizing apparatus
1325 components, there are additional health considerations that should be addressed in a PMTA for
1326 an e-liquid. In addition to the recommendations above for ENDS PMTAs in general, FDA
1327 recommends that you address the following additional information in the Product Analysis and
1328 Manufacturing section of a PMTA for an e-liquid.

1329
1330 **A. Components, Ingredients, and Additives**

1331
1332 In addition to the test analysis stated above in section VI.H.1.a, FDA recommends that you
1333 provide adequate information in the PMTA to characterize the constituents and other chemical
1334 constituents (e.g., menthol, glycerol) in the e-liquid and identify characteristics of the e-liquid
1335 that may impact the constituents in the aerosol. FDA also recommends that you provide the e-
1336 liquid design parameters that would be affected by and that would affect aerosolizing apparatus
1337 performance, such as the e-liquid viscosity and boiling point.

1338
1339 **B. Flavors**

1340
1341 Because of the potential impact of flavors on product toxicity and appeal to youth and young
1342 adults, scientific review, including toxicological review on flavor additives should be included in
1343 a PMTA for an e-liquid. There may be significant differences in the health risk of flavors
1344 depending on their route of exposure as well as the formation of additional chemicals due to
1345 heating or burning of the flavors. Substances that are generally recognized as safe (GRAS) under



1346 sections 201(s) and 409 of the FD&C Act (21 U.S.C. 348) are defined as substances that are
1347 intentionally added to food and intended for oral ingestion. E-liquid is not food or intended for
1348 oral ingestion; therefore, the fact that some substances have been designated GRAS for food
1349 does not mean that they are safe for inhalation.

1350
1351 Under section 910(b)(1)(A) of the FD&C Act, you must include in your PMTAs full reports of
1352 all information, published or known to, or which should be reasonably known to you (the
1353 applicant) concerning investigations that have been made to show the health risks of the new
1354 tobacco product and whether such new tobacco product presents less risk than other tobacco
1355 products. FDA considers the appeal and use of ENDS product flavors important to ascertain the
1356 health risks of these products. In this regard, FDA recommends that you describe research on
1357 flavor development including, but not limited to, market segmentation analysis or sensory
1358 testing. You should describe consumer perceptions among current ENDS users and other tobacco
1359 users for appeal and use intentions based on labeling and actual use of flavors, and product
1360 design.

1361
1362 **VIII. ADDITIONAL RECOMMENDATIONS FOR PREMARKET TOBACCO**
1363 **PRODUCT APPLICATIONS FOR AEROSOLIZING APPARATUS**

1364
1365 Aerosolizing apparatus have different properties and characteristics than e-liquids and,
1366 consequently, present additional health considerations that are important for you to address in a
1367 PMTA for an aerosolizing apparatus. In addition to the general recommendations above for
1368 ENDS PMTAs, FDA recommends that you address the following additional information in a
1369 PMTA for an aerosolizing apparatus.

1370
1371 **A. Aerosolizing Apparatus Design Factors to Consider**

1372
1373 Section 910(b)(1)(B) of the FD&C Act requires that a PMTA include a full statement of the
1374 components, ingredients, additives, and properties, and of the principle or principles of
1375 operation, of the new tobacco product. In addition, FDA recommends that in PMTAs for
1376 aerosolizing apparatus and their components sold separately, you address both the characteristics
1377 listed in this section of the guidance and the characteristics listed specifically for the batteries,
1378 atomizers, and software, as applicable.

1379
1380 ENDS product users and non-users are exposed to aerosols produced by the apparatus.
1381 Therefore, to understand the health impact of an ENDS product, it is important to understand
1382 how the e-liquid is heated as well as how the aerosol is generated and transmitted to the user.
1383 Information about the properties and principles of operation of an ENDS product will help FDA
1384 in determining the impact of the aerosol on health. FDA recommends that you provide a precise
1385 description of the aerosolizing apparatus, including detailed discussions of:

- 1386
1387
 - Aerosolizing apparatus features;
 - 1388 • Material and/or ingredient functions;
 - 1389 • Capabilities to monitor product performance (e.g., temperature sensing, voltage
1390 sensing, battery life detection);



- 1391 • Instructions and method of operation;
- 1392 • Materials of all aerosolizing apparatus components;
- 1393 • Operating ranges;
- 1394 • Power supply, such as batteries (including whether it is rechargeable or replaceable);
- 1395 • Charging source and the safety of using different charging sources; and
- 1396 • Heating source (e.g., heating coil, chemical reaction).

1397
1398 FDA also recommends that your PMTA contain detailed aerosolizing apparatus schematics (e.g.,
1399 CAD drawings) with dimensions, pictures, and labeling, accompanied by engineering design
1400 parameters.

1401
1402 Finally, electrical safety should be discussed, and applicable standards to which conformance
1403 have been demonstrated should be identified. This discussion should include appropriate data
1404 (e.g., test protocol, data, results). Additionally, you should provide a description of all built-in
1405 electrical safety features. Specific recommendations for batteries are listed in section VIII.B.1. If
1406 the product contains a controller, you should list and discuss the power management techniques
1407 used, such as pulse width modulation or direct current.

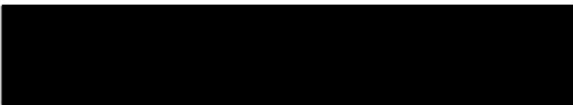
1408
1409 **B. Possible Design Parameters for Subcategories of Aerosolizing Apparatus**
1410 **Components and Parts**

1411
1412 FDA recognizes that there is no single set of engineering parameters that will characterize all
1413 aerosolizing apparatus, and that each subcategory may have additional design parameter
1414 information that is important in fully characterizing the health risk of the product. For example,
1415 battery characteristics such as alarm capabilities, voltage range, and battery type may affect the
1416 risk associated with using an ENDS product. The following sections provide examples of the
1417 information that FDA recommends you include for batteries, atomizers, and software. FDA
1418 recommends that these characteristics be addressed in a PMTA for an aerosolizing apparatus that
1419 includes the components discussed below and in a PMTA for the component, if sold separately.
1420 In situations where a PMTA is for an aerosolizing apparatus that is not sold with other
1421 components (e.g., an aerosolizing apparatus sold without the battery included), FDA
1422 recommends discussing specifications for the components that can be used in the aerosolizing
1423 apparatus. As noted, FDA recognizes that there are many more subcategories of aerosolizing
1424 apparatus components than the three mentioned here, but we have included examples for these
1425 three components to help guide applicants in submitting the general information FDA
1426 recommends including for aerosolizing apparatus components.

1427
1428 *1. Batteries*

1429
1430 FDA is concerned about the risk of the batteries in ENDS. Many different aspects of batteries
1431 can cause health risks, such as leaching of battery materials into the product, battery explosion,
1432 or other defects. To enable FDA to assess the risks of the battery to be used in your product, we
1433 recommend that your PMTA include the following information:

- 1434
- 1435 • If the aerosolizing apparatus includes the battery:



- 1436 ○ Amperage rating (i.e., the maximum suggested amperage to pull from the battery);
- 1437 ○ Battery mAh rating (i.e., the milliamps per hour of the battery and its correlation to
- 1438 battery life);
- 1439 ○ Battery type (including battery chemistry);
- 1440 ○ Voltage output (at full charge and at low charge); and
- 1441 ○ Testing certificates for any voluntary battery standards for the power supply.
- 1442 ● If the aerosolizing apparatus uses a consumer-replaceable battery:
- 1443 ○ Battery specifications required by the aerosolizing apparatus; and
- 1444 ○ Voltage range and wattage range, if the aerosolizing apparatus alters or regulates the
- 1445 voltage.
- 1446 ● If the aerosolizing apparatus has alarm capabilities, indicate whether the product
- 1447 includes:
- 1448 ○ Reverse polarity protection (i.e., does it protect the battery from being placed in the
- 1449 aerosolizing apparatus backwards);
- 1450 ○ Under-voltage lock-out protection (i.e., does the power lock out in the event of the
- 1451 voltage dropping below the operational value);
- 1452 ○ Over-voltage lock out protection (i.e., does the power lock out when the voltage in
- 1453 the circuit is raised above the design limit);
- 1454 ○ Low resistance protection (i.e., does the aerosolizing apparatus lock out if the wire
- 1455 resistance is too low and, if so, what is the low resistance limit);
- 1456 ○ High controller temperature protection (i.e., does the aerosolizing apparatus detect the
- 1457 temperature of the controller and shut off when the temperature is too high); and
- 1458 ○ Unintended activation protection such as a maximum activation time limit, on/off
- 1459 capability, and locking capabilities.

1460 2. *Atomizers*

1461
1462
1463 FDA recommends that, for PMTAs for aerosolizing apparatus with atomizers and atomizers sold
1464 separately, you address the properties for each of the components listed below.

- 1465
- 1466 ● Overall atomizer:
- 1467 ○ Draw resistance (and operable range if adjustable);
- 1468 ○ E-liquid capacity; and
- 1469 ○ Aerosol particle size across operable range.
- 1470 ● Coils:
- 1471 ○ Number of coils (either a set number or capability range, depending on aerosolizing
- 1472 apparatus design);
- 1473 ○ Coil gauge and material;
- 1474 ○ Coil resistance; and
- 1475 ○ Coil failure testing (i.e., cycles to failure).
- 1476 ● Wick:
- 1477 ○ Ignition temperature; and
- 1478 ○ Wicking absorbency (if refillable, we recommend that the absorbency be tested with
- 1479 low viscosity and high viscosity e-liquids).
- 1480



1481 3. *Software*

1482
1483 If the aerosolizing apparatus is software-driven, FDA recommends that you include the
1484 following:

- 1485 • A software description, including a summary of the features and software operating
1486 environment;
- 1487 • A hazard analysis of identified hardware/software hazards, including severity assessment
1488 and mitigations;
- 1489 • A software requirements specification, including a summary of functional requirements;
- 1490 • A traceability analysis, including traceability among requirements, specifications,
1491 identified hazards and mitigations, and verification and validation testing;
- 1492 • Verification and validation documentation, including software functional test plan,
1493 pass/fail criteria, and results; and
- 1494 • A revision level history, including revision history log with release version number and
1495 date.
1496

1497
1498 **IX. ADDITIONAL RECOMMENDATIONS FOR ENDS PRODUCTS THAT**
1499 **PACKAGE E-LIQUIDS AND AEROSOLIZING APPARATUS TOGETHER**

1500
1501 FDA recognizes that many ENDS products will be packaged and sold together. For example, an
1502 open aerosolizing apparatus, which does not contain e-liquids, may be packaged and sold with
1503 separately contained e-liquids. Similarly, a closed aerosolizing apparatus will contain the e-liquid
1504 in the apparatus. In both cases, FDA recommends that, in addition to the information discussed
1505 in section VI, you address those items discussed in section VII for e-liquids and section VIII for
1506 aerosolizing apparatus. Additionally, FDA recommends that product testing, such as testing
1507 aerosol particle size across the operable range, also be completed using the e-liquid solution and
1508 aerosolizing apparatus provided in the product package.

1509
1510 **X. CONSIDERATIONS FOR SCIENTIFIC STUDIES AND ANALYSES**

1511
1512 This guidance discusses FDA's current thinking on the types of information an applicant should
1513 include in a PMTA to help show that permitting such new tobacco product to be marketed would
1514 be appropriate for the protection of the public health. Throughout this guidance, we reference
1515 suggestions for scientific studies and analyses to support this showing. FDA believes that, in
1516 some cases, it may be possible to support a marketing order for an ENDS product without
1517 conducting new nonclinical or clinical studies: For example, if there is an established body of
1518 evidence regarding the health impact (individual or population) of your product or a similar
1519 product that can be adequately bridged to your product, such as data from the published literature
1520 or government-sponsored databases, these data may be sufficient to support a PMTA, as
1521 mentioned in the sections below.

1522
1523 In cases where a product's potential impact on the public health has not yet been sufficiently
1524 reviewed, new nonclinical and clinical studies may be required. The applicability of certain
1525 studies depends on what aspect of the statutory requirements of PMTA the applicant intends to



1526 address. For example, to bridge to a completed study, if the PMTA product has been studied only
1527 in a certain demographic, the applicant would need to demonstrate how the elements specific to
1528 showing that the product is appropriate for the protection of the public health also apply to
1529 different demographics that would be representative of the U.S. population as whole. Similarly,
1530 to use existing literature, if a similar product has been studied in a special population, this
1531 information may be used to support whether and how the product may be appropriate for the
1532 protection of the public health by providing data relevant to the special population, which we
1533 would not otherwise have absent a new clinical trial. In these cases, you should explain why the
1534 study is relevant to use for the PMTA product (e.g., the similarities between the product, product
1535 use, or product market).

1537 **A. Alternatives to U.S.-Conducted Randomized Controlled Clinical Trials**

1538
1539 Alternatives to U.S.-conducted randomized controlled clinical trials may be appropriate when
1540 potential bias associated with alternative controls can be addressed, including:

- 1542 • Valid non-U.S. randomized controlled clinical trials data (when data can be generalized
1543 to the U.S. population);
- 1544 • Study designs employing non-concurrent controls such as historical controls (e.g.,
1545 literature, subject records) or objective performance criteria (i.e., performance criteria
1546 based on broad sets of data from historical databases (e.g., literature, registries)) that are
1547 generally recognized as acceptable values (these criteria may be used for surrogate or
1548 clinical endpoints in demonstrating the risks or harm reduction for a tobacco product);
- 1549 • Observational studies; or
- 1550 • Scientifically valid surrogate endpoints (e.g., 1- or 2-year data as a predictor for long-
1551 term experience or health effects).

1552
1553 Similarly, an effective use of incorporating by reference other PMTA submissions that have been
1554 previously authorized for the same applicant and same product (rather than resubmitting
1555 duplicative information) may be done with cross-referencing. Alternatively, for information on
1556 master files, see Section X.D.

1557
1558 **B. Literature Reviews**

1559
1560 Published literature reviews (including meta-analysis) or reports may be acceptable to support a
1561 PMTA, but are considered a less robust form of support for a PMTA. Additionally, applicants
1562 may conduct their own meta-analysis as appropriate. If a literature review is used to support a
1563 PMTA, the PMTA should:

- 1565 • Describe the methodologies used in the literature review in detail and include the
1566 databases searched and the date of searches, search terms, reasons for inclusion/exclusion
1567 of documents, and the strategy for study quality assessment (systematic review is
1568 preferred);
- 1569 • Identify the specific question(s) and issue(s) addressed by the literature review;
- 1570 • Clearly identify the documents or manuscripts that address a specific question or issue;



- 1571 • Identify the funding source for included studies;
- 1572 • Identify study design and methods;
- 1573 • Identify characterization of study participants;
- 1574 • Identify the year and geographical location of studies;
- 1575 • Identify strengths and limitations of studies (e.g., study design elements including
- 1576 randomization details, potential biases, validity, variability, statistical models, and
- 1577 heterogeneity);
- 1578 • Provide an interpretation of study findings;
- 1579 • Provide adequate justification for bridging data from the product studied to your new
- 1580 tobacco product;
- 1581 • Provide a summary of the evidence from the literature review;
- 1582 • Document how the literature review findings support or do not support that your new
- 1583 tobacco product is appropriate for the protection of the public health;
- 1584 • Include a bibliography and an appendix with the referenced publications; and
- 1585 • Include comparative assessments of the health risks associated with use of your new
- 1586 tobacco product compared to the risks associated with quitting tobacco product use, using
- 1587 other tobacco products, and never using tobacco products.

1588
1589 In addition, when you submit a literature review to support an ENDS PMTA, FDA recommends
1590 that you consider the relevancy of the literature and adequacy of the study design in order to
1591 determine the likelihood that a particular body of literature will support a marketing order for the
1592 new tobacco product. For example, the following questions may be considered:

- 1593
- 1594 • Is the tobacco product in the literature comparable in terms of technology to the new
- 1595 tobacco product?
- 1596 • Are there data (e.g., range of possible use, emissions under conditions of use, biomarkers
- 1597 of exposure) that can be used to adequately demonstrate comparability?
- 1598 • Was the product in the literature used in a population that adequately represents the target
- 1599 population for the new tobacco product?
- 1600 • Is the information in the literature sufficient to determine how the tobacco product was
- 1601 used?

1602
1603 We recommend that, to strengthen the likelihood that the literature review will support your
1604 PMTA, you obtain additional information, such as full study methods, including randomization
1605 details.

1606 **C. Analysis of Published Literature and Public Datasets**

1607
1608
1609 You may consider conducting independent analyses of published studies. In these cases, FDA
1610 may review your analyses or publically available analyses (for which there may be limited access
1611 to data, limited access to detailed study reports, or limited access to both) to partially or entirely
1612 support a PMTA. Please note, however, that if critical study details are not submitted, the studies
1613 may not be useful in FDA's review of your PMTA.

1614



1615 If you cannot obtain the primary source data from the publically available literature, we
1616 recommend that, to the extent possible, you obtain other information, such as the protocol,
1617 records of trial conduct and procedures, subject data listings for key variables, and
1618 documentation of the statistical analysis. If adverse or unintended experiences are being
1619 monitored, we recommend that you capture and document complete information for all serious
1620 adverse experiences (including deaths) and subject withdrawal related to adverse experiences,
1621 toxicity, or both.

1622
1623 In addition, FDA intends to open public docket for uniquely identified compounds likely to be
1624 used in an e-liquid product, such as propylene glycol, glycerin, nicotine, colorants, and flavoring
1625 agents. FDA intends to invite stakeholders to submit to the docket information regarding
1626 specific compounds, including data, studies, or other files, such as data on individual health
1627 effects of inhalation exposure, animal study data examining exposure to varying levels of
1628 compounds within e-liquids, or testing the impact of temperature on changes to the aerosol
1629 constituents. This information could then be used to support a PMTA for ENDS products.

1631 **D. Master Files**

1632
1633 To reduce research burdens and increase efficiency of PMTA preparation and submissions, we
1634 encourage you to use tobacco product master files (TPMFs) whenever possible. A master file
1635 may contain detailed information on a specific manufacturing facility, process, methodology, or
1636 component used in the manufacturing, processing, or packaging of a tobacco product. By
1637 obtaining permission from a master file holder, you may reference extensive ingredient lists and
1638 constituent testing or other information that you otherwise would be required to perform or
1639 develop yourself to support your PMTA. Refer to FDA's guidance for industry, *Tobacco*
1640 *Product Master Files*, for more information on using TPMFs.

1641 **E. Bridging**

1642
1643 Ideally, a PMTA will include studies conducted using the new tobacco product; however,
1644 bridging of data from one product to another may be feasible for a subset of products or for
1645 certain types of clinical studies. For example, "X-flavor" e-liquids with nicotine concentrations
1646 ranging from 1 milligram per milliliter (mg/mL) to 24 mg/mL may not require unique studies for
1647 each nicotine concentration of the "X-flavor" product if data from a subset of nicotine
1648 concentrations (e.g., low, middle, high) of "X-flavor" products may be bridged to other
1649 concentrations of "X-flavor" products. If you choose to bridge data from a studied tobacco
1650 product to your new tobacco product, you should provide the rationale and justification to
1651 support bridging (e.g., why the data used are applicable to your new tobacco product).

1652
1653 In addition, in certain circumstances, information that is available from earlier versions of the
1654 same ENDS product, or from marketing experience with similar tobacco products, may be used
1655 to bridge studies and analyses for the purposes of an ENDS PMTA. Earlier generations of a
1656 product line may provide important information that can reduce the need for large amounts of
1657 additional data.

1658
1659



1660 While bridging your new tobacco product to existing data is a viable option, there may be
1661 circumstances when a bridging study may need to be conducted, such as when the product is
1662 sensitive to intrinsic factors (e.g., gender, race, age, pathology) and extrinsic factors (e.g.,
1663 environmental, cultural). If the product is insensitive to these factors, a new bridging study may
1664 not be necessary. Another example of when a bridging study may be needed is when the location
1665 or region of a study differs from the intended locations or regions where the product will be used.

1666

1667 **XI. POSTMARKET REQUIREMENTS**

1668

1669 A marketing order under section 910(c)(1)(A)(i) of the FD&C Act may require that the sale and
1670 distribution of the tobacco product be restricted, but only to the extent that the sale and
1671 distribution of a tobacco product may be restricted under a regulation under section 906(d). In
1672 addition, under section 910(f) of the FD&C Act, FDA may require that you establish and
1673 maintain certain postmarket records and make certain postmarket reports to FDA.

1674

1675 **XII. OFFICE OF SMALL BUSINESS ASSISTANCE**

1676

1677 Small businesses may contact [REDACTED] or by [REDACTED]
1678 [REDACTED] to discuss questions regarding PMTA content, such as information necessary to
1679 satisfy the filing criteria under section 910(b) of the FD&C Act or ways to reduce burden by
1680 reference to another submission via the TPMF process.

