

# Guidance for Industry

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## Modified Risk Tobacco Product Applications

### *DRAFT GUIDANCE*

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For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9:00 a.m. – 4:00 p.m. EDT.

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

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# Guidance for Industry<sup>1</sup>

## Modified Risk Tobacco Product Applications

*This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

### I. Introduction

This draft guidance provides information about submitting applications for modified risk tobacco products under section 911 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387k), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31). Congress found that “[u]nless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health . . .” Section 2(37) of the Tobacco Control Act. Furthermore, Congress noted that “[t]he dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that [FDA must] ensur[e] that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product.” Section 2(40) of the Tobacco Control Act. Thus, Congress recognized that manufacturers must “demonstrate that such products . . . meet a series of rigorous criteria, and will benefit the health of the population as a whole” before marketing tobacco products for use to reduce harm or the risk of tobacco-related disease or to reduce exposures to harmful substances associated with tobacco products. Section 2(36) of the Tobacco Control Act.

The modified risk tobacco product provisions of the FD&C Act may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use, particularly if companies take advantage of these provisions by making

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

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36 bold, innovative product changes that substantially reduce, or even eliminate altogether,  
37 either the toxicity or addictiveness of tobacco products, or both.

38  
39 Section 911(l)(1) of the FD&C Act directs FDA to issue regulations or guidance (or any  
40 combination thereof) on the scientific evidence required for assessment and ongoing  
41 review of modified risk tobacco products. This draft guidance, issued pursuant to section  
42 911(l)(1), explains, among other things:

- 43
- 44 • Who may submit a modified risk tobacco product application under section 911 of
  - 45 the FD&C Act;
  - 46 • When to submit a modified risk tobacco product application;
  - 47 • What information the FD&C Act requires you to submit in a modified risk
  - 48 tobacco product application;
  - 49 • What scientific studies and analyses FDA recommends you submit in a modified
  - 50 risk tobacco product application;
  - 51 • What information should be collected through postmarket surveillance and
  - 52 studies; and
  - 53 • How to organize and submit a modified risk tobacco product application.
- 54

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

60  
61 This document provides extensive information about the types of scientific studies and  
62 analyses FDA recommends that applicants consider conducting in order to provide the  
63 evidence needed to support issuance of an order under section 911(g) of the FD&C Act.  
64 As with all guidance, applicants can use an alternative approach if that approach would  
65 provide the evidence needed to support issuance of an order. FDA encourages anyone  
66 who is considering development of, or preparing an application for, a modified risk  
67 tobacco product to meet with FDA to discuss what studies would be appropriate for your  
68 product, so that you can best use your resources to conduct studies that will support your  
69 application. We request comment on the extent of information needed to support FDA’s  
70 decision-making process under section 911(g) of the FD&C Act.

71 **II. Background**

72  
73 Modified risk tobacco products (MRTPs) are tobacco products that are sold or distributed  
74 for use to reduce harm or the risk of tobacco-related disease associated with  
75 commercially marketed tobacco products (see Definitions).

76  
77 Before an MRTP can be introduced or delivered for introduction into interstate  
78 commerce, an order from FDA under section 911(g) of the FD&C Act (“risk

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79 modification order” or “exposure modification order” – see Definitions) must be in effect  
80 with respect to the tobacco product. Section 911(a) of the FD&C Act. If the modified  
81 risk tobacco product is a new tobacco product within the meaning of section 910(a)(1),  
82 any applicable premarket review requirements under section 910 of the FD&C Act must  
83 also be satisfied. Section 910(a)(2)(A) of the FD&C Act.

84  
85 Section 911(g) of the FD&C Act describes the demonstrations applicants must make to  
86 obtain an order from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two  
87 bases for FDA to issue an order.

88  
89 In general, FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk  
90 modification order) only if it determines the applicant has demonstrated that the product,  
91 as it is actually used by consumers, will:

- 92
- 93 • Significantly reduce harm and the risk of tobacco-related disease to individual  
94 tobacco users; and
  - 95 • Benefit the health of the population as a whole taking into account both users of  
96 tobacco products and persons who do not currently use tobacco products.
- 97

98 Section 911(g)(1) of the FD&C Act.

99  
100 FDA has the authority to require with respect to tobacco products for which risk  
101 modification orders are issued that the product comply with requirements relating to  
102 advertising and promotion of the tobacco product. Section 911(h)(5) of the FD&C Act.

103  
104 In the alternative, for products that cannot receive a risk modification order from FDA  
105 under section 911(g)(1) of the FD&C Act, FDA may issue an order under section  
106 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the  
107 applicant has demonstrated that:

- 108
- 109 • Such an order would be appropriate to promote the public health;
  - 110 • Any aspect of the label, labeling, and advertising for the product that would cause  
111 the product to be a modified risk tobacco product is limited to an explicit or  
112 implicit representation that the tobacco product or its smoke does not contain or is  
113 free of a substance or contains a reduced level of a substance, or presents a  
114 reduced exposure to a substance in tobacco smoke;
  - 115 • Scientific evidence is not available and, using the best available scientific  
116 methods, cannot be made available without conducting long-term epidemiological  
117 studies for an application to meet the standards for obtaining an order under  
118 section 911(g)(1); and
  - 119 • The scientific evidence that is available without conducting long-term  
120 epidemiological studies demonstrates that a measurable and substantial reduction  
121 in morbidity or mortality among individual tobacco users is reasonably likely in  
122 subsequent studies.
- 123

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124 Section 911(g)(2)(A) of the FD&C Act.

125

126 Furthermore, for FDA to issue an exposure modification order, FDA must find that the  
127 applicant has demonstrated that:

128

129 • The magnitude of overall reductions in exposure to the substance or substances  
130 which are the subject of the application is substantial, such substance or  
131 substances are harmful, and the product as actually used exposes consumers to the  
132 specified reduced level of the substance or substances;

133 • The product as actually used by consumers will not expose them to higher levels  
134 of other harmful substances compared to the similar types of tobacco products  
135 then on the market unless such increases are minimal and the reasonably likely  
136 overall impact of use of the product remains a substantial and measurable  
137 reduction in overall morbidity and mortality among individual tobacco users;

138 • Testing of actual consumer perception shows that, as the applicant proposes to  
139 label and market the product, consumers will not be misled into believing that the  
140 product is or has been demonstrated to be less harmful or presents or has been  
141 demonstrated to present less of a risk of disease than one or more other  
142 commercially marketed tobacco products; and

143 • Issuance of the exposure modification order is expected to benefit the health of  
144 the population as a whole taking into account both users of tobacco products and  
145 persons who do not currently use tobacco products.

146

147 Section 911(g)(2)(B) of the FD&C Act.

148

149 In evaluating the benefit to health of individuals and of the population as a whole under  
150 sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

151

152 • The relative health risks the modified risk tobacco product presents to  
153 individuals;

154 • The increased or decreased likelihood that existing tobacco product users who  
155 would otherwise stop using such products will switch to using the modified risk  
156 tobacco product;

157 • The increased or decreased likelihood that persons who do not use tobacco  
158 products will start using the modified risk tobacco product;

159 • The risks and benefits to persons from the use of the modified risk tobacco  
160 product compared to the use of smoking cessation drug or device products  
161 approved by FDA to treat nicotine dependence; and

162 • Comments, data, and information submitted to FDA by interested persons.

163

164 Section 911(g)(4) of the FD&C Act.

165

166 In reviewing any MRTPA and making its determination whether to grant an order under  
167 section 911(g) of the FD&C Act, FDA will consider the scientific evidence submitted by

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168 the applicant as well as other scientific evidence or information made available to FDA.  
169 Section 911(g)(3) of the FD&C Act.

170  
171 Furthermore, FDA must ensure, for a risk or exposure modification order, that the  
172 advertising and labeling of the MRTP enable the public to comprehend the information  
173 concerning modified risk and to understand the relative significance of such information  
174 in the context of total health and in relation to all of the tobacco-related diseases and  
175 health conditions. Section 911(h)(1) of the FD&C Act.

176  
177 A risk modification order issued under section 911(g)(1) of the FD&C Act will be  
178 effective for the period of time specified in the order issued by FDA. Section 911(h)(4)  
179 of the FD&C Act. An applicant to whom a risk modification order is issued under  
180 section 911(g)(1) must conduct postmarket surveillance and studies and submit the  
181 results of such surveillance and studies to FDA annually. Section 911(i)(1) of the FD&C  
182 Act.

183  
184 An exposure modification order issued under section 911(g)(2) of the FD&C Act will be  
185 effective for a term of not more than 5 years. FDA may renew an exposure modification  
186 order if the applicant files a new application and FDA finds that the requirements for  
187 such order under section 911(g)(2) continue to be satisfied. Section 911(g)(2)(C)(i) of  
188 the FD&C Act. Further, an exposure modification order will be conditioned on the  
189 applicant’s agreement to conduct postmarket surveillance and studies and to submit the  
190 results of such surveillance and studies to FDA annually. Section 911(g)(2)(C)(ii), (iii)  
191 of the FD&C Act.

### 192 **III. Definitions**

193  
194 This section provides definitions of certain terms used in this guidance.

#### 195 **A. Tobacco Product**

196  
197 “Tobacco product” means “any product made or derived from tobacco that is intended for  
198 human consumption, including any component, part, or accessory of a tobacco product  
199 (except for raw materials other than tobacco used in manufacturing a component, part, or  
200 accessory of a tobacco product).” Section 201(rr)(1) of the FD&C Act (21 U.S.C.  
201 321(rr)(1)). Thus, the term is not limited to products containing tobacco, but also includes  
202 components, parts, or accessories of tobacco products, whether they are sold for further  
203 manufacturing or for consumer use. For example, cigarette rolling papers and filters are  
204 tobacco products, whether they are sold to consumers for use with roll-your- own tobacco  
205 or are sold for further manufacturing into a product sold to a consumer, such as a  
206 cigarette. This term does not include an article that is a drug, a device, or a combination  
207 product as defined in the FD&C Act. Section 201(rr)(2) of the FD&C Act (21 U.S.C.  
208 321(rr)(2)).



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209 **B. New Tobacco Product**

210

211 “New tobacco product” means “any tobacco product (including those products in test  
212 markets) that was not commercially marketed in the United States as of February 15,  
213 2007; or any modification (including a change in design, any component, any part, or any  
214 constituent, including a smoke constituent, or in the content, delivery or form of nicotine,  
215 or any other additive or ingredient) of a tobacco product where the modified product was  
216 commercially marketed in the United States after February 15, 2007.” Section 910(a)(1)  
217 of the FD&C Act (21 U.S.C. 387j(a)(1)).

218 **C. Modified Risk Tobacco Product**

219

220 “Modified risk tobacco product” means any tobacco product that is sold or distributed for  
221 use to reduce harm or the risk of tobacco-related disease associated with commercially  
222 marketed tobacco products. Section 911(b)(1) of the FD&C Act. Sold or distributed for  
223 use to reduce harm or the risk of tobacco-related disease associated with commercially  
224 marketed tobacco products means a tobacco product

225

226 (1) that represents in its label, labeling, or advertising, either implicitly or  
227 explicitly, that:

228

229 i. the tobacco product presents a lower risk of tobacco-related disease or  
230 is less harmful than one or more other commercially marketed tobacco  
231 products;

232

233 ii. the tobacco product or its smoke contains a reduced level of a  
234 substance or presents a reduced exposure to a substance; or

235

236 iii. the tobacco product or its smoke does not contain or is free of a  
237 substance;

238

239 (2) that uses the descriptors “light”, “mild”, “low”, or similar descriptors in its  
240 label, labeling, or advertising;<sup>2</sup> or

241

242 (3) for which the tobacco product manufacturer has taken any action directed to  
243 consumers through the media or otherwise, other than by means of the  
244 tobacco product’s label, labeling, or advertising, after June 22, 2009,  
245 respecting the product that would be reasonably expected to result in  
246 consumers believing that the tobacco product or its smoke may present a  
247 lower risk of disease or is less harmful than one or more commercially  
248 marketed tobacco products.

249

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251

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<sup>2</sup> While cigarettes had been marketed with such descriptors before the Tobacco Control Act was enacted, as of June 22, 2010, manufacturers were prohibited from manufacturing for sale or distribution any tobacco products for which the label, labeling, or advertising contains the descriptors “light,” “low,” or “mild,” or any similar descriptor, without an FDA order in effect under section 911(g) of the FD&C Act. Section 911(b)(3) of the FD&C Act. Furthermore, as of July 22, 2010, manufacturers, including importers of finished tobacco products, were prohibited from introducing into the domestic commerce of the United States any tobacco product for which the label, labeling, or advertising contains the descriptors “light,” “low,” or “mild,” or any similar descriptor, irrespective of the date of manufacture, without an FDA order in effect under section 911(g) of the FD&C Act. *Id.*

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243 marketed tobacco products, or presents a reduced exposure to, or does not  
244 contain or is free of, a substance or substances.

245  
246 Section 911(b)(2) of the FD&C Act.<sup>3</sup>

247  
248 A product that is intended to be used for the treatment of tobacco dependence, including  
249 smoking cessation, is not a modified risk tobacco product if it has been approved as a  
250 drug or device by FDA and is subject to the requirements of chapter V of the FD&C Act.  
251 Section 911(c) of the FD&C Act.

252 **D. Risk Modification Order**

253  
254 A risk modification order is an order permitting the introduction or delivery for  
255 introduction into interstate commerce of a modified risk tobacco product that FDA has  
256 found meets the criteria for an order under section 911(g)(1) of the FD&C Act. In order  
257 for FDA to issue a risk modification order under section 911(g)(1) of the FD&C Act, the  
258 applicant must demonstrate that the product, as it is actually used by consumers, will:

- 259
- 260 • Significantly reduce harm and the risk of tobacco-related disease to individual
  - 261 tobacco users; and
  - 262 • Benefit the health of the population as a whole taking into account both users of
  - 263 tobacco products and persons who do not currently use tobacco products.
- 264

265 FDA intends to describe in the risk modification order the claim(s) for the tobacco  
266 product covered by the order.

267 **E. Exposure Modification Order**

268  
269 An exposure modification order is an order permitting the introduction or delivery for  
270 introduction into interstate commerce of a modified risk tobacco product that reduces or  
271 eliminates exposure to a substance and for which the available scientific evidence  
272 suggests that a measurable and substantial reduction in morbidity and mortality is  
273 reasonably likely to be demonstrated in future studies. In order for FDA to issue an  
274 exposure modification order, the applicant must satisfy all of the criteria for issuance of  
275 an order under section 911(g)(2) of the FD&C Act. An applicant may file an application  
276 seeking an exposure modification order only if scientific evidence is not available and,  
277 using the best available scientific methods, cannot be made available without conducting  
278 long-term epidemiological studies, for an application to meet the standards set forth in  
279 section 911(g)(1).

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<sup>3</sup> No smokeless tobacco product shall be considered to be sold or distributed for use to reduce harm or the risk of tobacco-related disease solely because its label, labeling, or advertising uses the following phrases: “smokeless tobacco,” “smokeless tobacco product,” “not consumed by smoking,” “does not produce smoke,” “smokefree,” “smoke-free,” “without smoke,” “no smoke,” or “not smoke.” Section 911(b)(2)(C) of the FD&C Act.

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280

281 If an applicant is seeking an exposure modification order, any aspect of the label,  
282 labeling, and advertising that would cause the tobacco product to be an MRTP must be  
283 limited to an explicit or implicit representation that:

284

- 285 • The tobacco product or its smoke does not contain or is free of a substance;
- 286 • The tobacco product or its smoke contains a reduced level of a substance; or
- 287 • The tobacco product presents a reduced exposure to a substance in tobacco  
288 smoke.

289

290 FDA intends to describe in the exposure modification order the claim(s) for the tobacco  
291 product covered by the order.

292 **IV. General Information**

293 **A. Who Submits an MRTPA?**

294

295 Any person may submit an application seeking an order under section 911(g) of the  
296 FD&C Act. The requirements of section 911 of the FD&C Act apply to any tobacco  
297 product subject to Chapter IX of the FD&C Act that meets the definition of an MRTP.

298

299 Tobacco products subject to Chapter IX of the FD&C Act include the products named in  
300 section 901(b) (i.e. cigarettes, cigarette tobacco, smokeless tobacco and roll-your-own  
301 tobacco) and tobacco products that have been or may be deemed by regulation to be  
302 subject to Chapter IX of the FD&C Act (section 901(b) of the FD&C Act), as well as the  
303 components, parts, and accessories of such products (e.g., cigarette rolling papers, filters,  
304 or filter tubes sold separately or as part of kits) sold or distributed for consumer use or for  
305 further manufacture.

306

307 At this time, FDA does not intend to enforce the requirements of section 911 of the  
308 FD&C Act for components, parts, or accessories of regulated tobacco products that are  
309 both (1) sold or distributed for further manufacturing into finished tobacco products, and  
310 (2) not sold or promoted to consumers.

311 **B. When Should You Submit an MRTPA?**

312

313 Before you may introduce or deliver for introduction into interstate commerce an MRTP,  
314 there must be in effect an order under section 911(g) of the FD&C Act. FDA encourages  
315 persons to meet with FDA early in their process of developing an MRTP to discuss  
316 MRTPA submission and investigational requirements and recommendations. See section  
317 IX.B.

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319 *Other Required Submissions*

320

321 If your proposed MRTP is a new tobacco product within the meaning of section  
322 910(a)(1), it is subject to any applicable premarket review requirements under section  
323 910 of the FD&C Act, *in addition to* any requirements under section 911 of the FD&C  
324 Act. To introduce or deliver for introduction a new tobacco product into interstate  
325 commerce there must be:

326

- 327 • A substantial equivalence order under section 910(a)(2)(i) of the FD&C Act in  
328 effect for the tobacco product;
- 329 • An exemption of the tobacco product from the requirement to obtain a substantial  
330 equivalence order under section 910(a)(2)(i) of the FD&C Act pursuant to a  
331 regulation issued under section 905(j)(3) of the FD&C Act; or
- 332 • A marketing authorization order issued by FDA for the tobacco product under  
333 section 910(c)(1)(A)(i) of the FD&C Act.

334

335 The label and packaging of a tobacco product are considered a “part” of that product. A  
336 change to any part of a tobacco product after February 15, 2007, makes that product a  
337 “new tobacco product.”<sup>4</sup> Adding modified risk claims to the label or packaging of a  
338 tobacco product that is already commercially marketed makes the tobacco product a new  
339 tobacco product. Therefore, in addition to obtaining an order from FDA under section  
340 911(g) of the FD&C Act, the applicant must satisfy the applicable premarket review  
341 requirements under section 910 of the FD&C Act.

342

343 For details on how to submit a substantial equivalence report under section 905(j) of the  
344 FD&C Act (21 U.S.C. 387e(j)), see FDA’s Guidance for Industry *Section 905(j) Reports:  
345 Demonstrating Substantial Equivalence for Tobacco Products*  
346 ([http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInfor  
347 mation/UCM239021.pdf](http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf)) and FDA’s Draft Guidance for Industry *Demonstrating the  
348 Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked  
349 Questions*  
350 ([http://www.fda.gov/downloads/TobaccoProducts/ResourcesforYou/ForIndustry/UCM27  
351 1239.pdf](http://www.fda.gov/downloads/TobaccoProducts/ResourcesforYou/ForIndustry/UCM271239.pdf)). For details on how to request an exemption from the substantial equivalence  
352 requirements, see FDA’s final rule – *Exemptions from Substantial Equivalence  
353 Requirements for Tobacco Products* (76 FR 38961; July 5, 2011)  
354 (<http://www.gpo.gov/fdsys/pkg/FR-2011-07-05/pdf/2011-16766.pdf>). For details on how  
355 to submit a Premarket Tobacco Product Application (PMTA) under section 910(b) of the  
356 FD&C Act (21 U.S.C. 387j(b)), see FDA’s Draft Guidance for Industry *Applications for  
357 Premarket Review of New Tobacco Products*

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<sup>4</sup> See FDA’s Draft Guidance for Industry *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions*. As discussed in this draft guidance, however, we do not intend to enforce the premarket requirements of sections 905(j) and 910 of the FD&C Act for certain limited modifications to labels and packaging (e.g., if modifications are made to comply with warning label requirements of the Tobacco Control Act).

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358 [http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInfor](http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM273425.pdf)  
359 [mation/UCM273425.pdf](http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM273425.pdf).

360 **C. Can I Introduce or Deliver for Introduction into Interstate**  
361 **Commerce an MRTP Without an Order Under Section 911(g) in**  
362 **Effect?**

363  
364 No. Such activity would violate section 911 of the FD&C Act, which provides that an  
365 MRTP may not be introduced or delivered for introduction into interstate commerce  
366 without an order under section 911(g) in effect with respect to such product. Section  
367 911(a) of the FD&C Act.

368  
369 Under section 301(pp) of the FD&C Act (21 U.S.C. 331(pp)), introduction or delivery for  
370 introduction into interstate commerce of a tobacco product in violation of section 911 is a  
371 prohibited act. In addition, under section 902(8) of the FD&C Act (21 U.S.C. 387b(8)), a  
372 tobacco product is deemed adulterated if it is in violation of section 911 of the FD&C  
373 Act, and the introduction or delivery for introduction into interstate commerce of any  
374 adulterated tobacco product is also a prohibited act. Section 301(a) of the FD&C Act (21  
375 U.S.C. 331(a)). Violations of the FD&C Act are subject to regulatory and enforcement  
376 action by FDA, including, but not limited to, seizure and injunction. Note, however, that  
377 section 911 only applies to MRTPs; a responsible entity can introduce a new tobacco  
378 product *without* modified risk claims into interstate commerce so long as they satisfy the  
379 applicable premarket review requirements under section 910 of the FD&C Act.  
380

381 **V. Contents of an MRTPA**

382 **A. Contents of an MRTPA Required Under Section 911(d)**

383  
384 Under section 911(d) of the FD&C Act, you must provide the following information in  
385 your MRTPA:<sup>5</sup>  
386

- 387
- 388 • A description of the proposed product and any proposed advertising and labeling;
  - 389 • The conditions for using the product;
  - 390 • The formulation of the product;
  - 391 • Sample product labels and labeling;
  - 392 • All documents (including underlying scientific information) relating to research  
393 findings conducted, supported, or possessed by the tobacco product manufacturer  
394 relating to the effect of the product on tobacco-related diseases and health-related  
395 conditions, including information both favorable and unfavorable to the ability of  
the product to reduce risk or exposure and relating to human health; and

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<sup>5</sup> Under section 911(d)(7) of the FD&C Act, FDA has the authority to require the submission of additional information.

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- 396       • Data and information on how consumers actually use the tobacco product.

397

398 This subsection (V.A) describes information that the Agency recommends you submit for  
399 each category of information required by section 911(d)(1)-(6) of FD&C Act. Section  
400 VI, in contrast, describes the information that you are required to submit, or that the  
401 Agency recommends you submit, to support the scientific demonstrations necessary for  
402 the issuance of an order under section 911(g) of the FD&C Act.

403           **1. A Description of the Proposed Tobacco Product and Any Proposed**  
404           **Advertising and Labeling**

405

406 You must include in your application a description of the product and any proposed  
407 advertising and labeling. Section 911(d)(1) of FD&C Act.

408

409 FDA recommends that your description of the proposed product include the following  
410 information:

411

- 412       • The brand name and, if applicable, subbrand name of the proposed modified risk  
413 tobacco product;
- 414       • A description of the product form (e.g., traditional cigarette, shredded tobacco,  
415 inhaler, liquid, gel, dissolvable strip, stick, or tablet);
- 416       • A description of the product dimensions and the overall construction of the  
417 product (using a diagram or schematic drawing that clearly depicts the finished  
418 product and its components with dimensions, operating parameters, and  
419 materials);
- 420       • Whether the product uses a heating source and, if so, a description of the heat  
421 source (e.g., burning coal or other substance, electric, chemical reaction, carbon  
422 tip);
- 423       • A description of all design features of the product<sup>6</sup> (e.g., location of ventilation  
424 holes, heat source, paper porosity, coatings, nicotine concentration gradient); and
- 425       • Any other information relevant to describing the tobacco product, such as whether  
426 the tobacco product requires special handling or storage.

427

428 FDA recommends that your description of proposed advertising and labeling include the  
429 following information, which is important in evaluating whether the product will benefit  
430 the health of the population as a whole (section 911(g)(1)(B) and (g)(2)(B)(iv) of the  
431 FD&C Act) and how consumers understand the risks posed by the product as the  
432 applicant proposes to label and market it (section 911(g)(2)(B)(iii) and (h)(1) of the  
433 FD&C Act):

434

- 435       • Copies of any draft promotional materials (e.g., advertising and labeling)  
436 developed by the time of filing that the applicant expects will be used in  
437 marketing the MRTP. FDA recognizes that some promotional materials may be

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<sup>6</sup> Numerical levels should be supplied, where appropriate.

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438 derivative of other materials submitted in the application, representing only minor  
439 differences in layout or format, or displaying a different health warning than  
440 material submitted in the application. Such derivative materials may be omitted;  
441 and,

- 442 • A description of how you intend to communicate the proposed modified risk  
443 claim(s) to consumers, including any actions directed to consumers that the  
444 tobacco product manufacturer or distributor of the tobacco product plans to take  
445 to communicate the proposed modified risk claim(s) to consumers (other than by  
446 means of the product label, labeling, or advertising).

447 **2. The Conditions for Using the Tobacco Product**

448  
449 You must provide as part of your application “the conditions for using the product.”  
450 Section 911(d)(2) of the FD&C Act. FDA recommends that you include the following  
451 information on conditions for using the product:

- 452  
453 • A full narrative description of the way in which a consumer will use the tobacco  
454 product, including a description of how a consumer operates the product (e.g.,  
455 whether a consumer places the tobacco product in the mouth or nose, whether a  
456 consumer ignites the tobacco product and by what means, whether the product is  
457 designed to be smoked, inhaled, swallowed, dissolved, sniffed, chewed, etc.);
- 458 • A description of the length of time it takes a consumer to consume a single unit of  
459 the product. The description should be quantitative in nature and include  
460 information about the pattern of use during that time (i.e., intermittent or  
461 continuous);
- 462 • Specific instructions on how to use and store the product to get the proposed  
463 reduction in risk or exposure; and
- 464 • Specific instructions on how to avoid using the product in a way that could reduce  
465 or eliminate the potential benefit or increase the risk of using the product.

466 **3. The Formulation of the Tobacco Product**

467  
468 You must submit as part of your application, “the formulation of the product.” Section  
469 911(d)(3) of the FD&C Act. In submitting the formulation of your product, FDA  
470 recommends that you include the following:

- 471  
472 • A complete list of uniquely identified components, ingredients, and additives by  
473 quantity in your tobacco product as well as the applicable specifications and a  
474 description of the intended function for each.<sup>7</sup> Components, ingredients, and

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<sup>7</sup> For guidance on uniquely identifying components, ingredients, and additives and reporting their quantities, refer to FDA’s Guidance for Industry *Listing of Ingredients in Tobacco Products* (<http://www.fda.gov/downloads/TobaccoProduct/GuidanceComplianceRegulatoryInformation/UCM192053.pdf>). If you have previously submitted this information under another section of the FD&C Act (e.g., a listing of ingredients or new tobacco product application), you can reference that submission in your MRTPA.

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475 additives include anything that may reasonably be expected, directly or indirectly,  
476 to become part of, or affect the characteristics of, the finished tobacco product.  
477 This includes, but is not limited to tobacco, paper, glue, flavorings, burn-rate  
478 controllers, and pH modifiers;

- 479 • A description of tobacco blending, reconstitution, or manipulation;
- 480 • A description of manufacturing steps, including the sources of all components,  
481 and quality control measures in place. The applicant should provide sufficient  
482 detail to assure FDA that the product meets manufacturing specifications and that  
483 it may be manufactured in a consistent manner that minimizes the variability in  
484 levels of exposures and/or risk to users/nonusers across occasions of use;
- 485 • A description of how the design, materials, ingredients, and heating source (if  
486 applicable) combine to produce the final product;
- 487 • A quantitative description of the performance criteria for the tobacco product  
488 (e.g., burn rate, ventilation criteria, dissolution rate); and
- 489 • Data establishing the stability of the product through the stated shelf life.

490

491 FDA recommends that the list of components, ingredients, and additives contain all items  
492 used in the synthesis, extraction, and/or preparation of the product, regardless of whether  
493 the items are found in the final the product. You should list ingredients by component of  
494 the tobacco product, including:

495

- 496 ○ Chemical Abstract Service number, where applicable;
- 497 ○ Function and purpose;
- 498 ○ Unit of measure; and
- 499 ○ Level used in tobacco product.

500

**4. Sample Product Labels and Labeling**

501

502 You must include in your application “sample product labels and labeling.” Section  
503 911(d)(4) of the FD&C Act. You should include copies of each package label variation  
504 (including inserts and onserts) that is proposed to be used for the modified risk tobacco  
505 product, except that you may omit copies of package label variations for each health  
506 warning required by law.

507

**5. All Documents Relating to Research Findings**

508

509 You must include in your application all documents (including underlying scientific  
510 information) relating to research findings conducted, supported<sup>8</sup>, or possessed<sup>9</sup>, by the

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<sup>8</sup> FDA considers a person to have supported a study if the person in any way provides assistance for the conduct of the study (e.g., by providing funding, personnel or other resources, protocols, product, etc.).

<sup>9</sup> FDA considers research findings possessed to include findings from studies not conducted or supported by the manufacturer, but which it has received, or has reviewed to inform the development of the modified risk tobacco product.



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511 tobacco product manufacturer<sup>10</sup> relating to the effect of the product on tobacco-related  
512 diseases and health-related conditions, including information both favorable **and**  
513 unfavorable to the ability of the product to reduce risk or exposure and relating to human  
514 health. Section 911(d)(5) of the FD&C Act. The documents required to be submitted  
515 under section 911(d)(5) may include documents not in the possession of the tobacco  
516 product manufacturer. We request that you submit a description of the procedures you  
517 used to collect documents to comply with section 911(d)(5) as well as a list of the entities  
518 and individuals from whom you retrieved or attempted to retrieve documents.

519

520 You should submit documents relating to research findings from studies conducted both  
521 within and outside the United States. See section IX.C for further discussion on the use  
522 of studies conducted outside the United States in support of an MRPTA.

523

524 In general, for guidance on what constitutes a “document” and otherwise submitting “all  
525 documents . . . relating to research finding” refer to FDA’s Guidance for Industry

526 *Tobacco Health Document Submission*

527 ([http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInfor](http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM208916.pdf)  
528 [mation/UCM208916.pdf](http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM208916.pdf)).

529

530 FDA expects that the applicant will include, among other things, as part of its submission  
531 of relevant documents:

532

- 533 • Study reports,
- 534 • Study protocols, and
- 535 • Raw data (in electronic format, where available, with instructions about its use).

536

537 If any of this information is not available, applicants should provide an explanation for  
538 the omission.

539

540 Additionally, if the applicant is aware of relevant research findings not conducted,  
541 supported, or possessed by the tobacco manufacturer, we ask that the applicant include  
542 copies of the research findings. Alternatively, if the research findings are found in  
543 published literature, applicants can submit a bibliography.

544

545 Further guidance regarding how to organize your scientific studies and analyses for  
546 submission to FDA is provided in section VIII.A.7.

547 **6. Data and Information on How Consumers Actually Use the Tobacco**  
548 **Product**

549

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<sup>10</sup> You should include documents related to research findings conducted, supported, or possessed by entities that are the same, related, or affiliated with the tobacco product manufacturer, as well as any of the tobacco manufacturer’s predecessors in interest.

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550 You must include in your application data and information on how consumers actually  
551 use the tobacco product. Section 911(d)(6) of the FD&C Act. In providing this  
552 information, FDA recommends that you include data generated from consumer use in  
553 both controlled situations in which the subjects' use can be closely monitored, and natural  
554 environments in which the subjects may use the product as they would without the  
555 limitations inherent in a controlled setting. FDA recommends that the data and  
556 information provided address:

557

- 558 • Whether consumers can and are likely to comply with any instructions for  
559 product use;
- 560 • The number of units of the product consumed per day (e.g., cigarettes per day)  
561 and the way in which individuals consume each unit of the product (e.g., puffing  
562 profiles); and
- 563 • Concurrent use of multiple products containing nicotine or tobacco.

564 **B. Other Information**

565

566 FDA may request other information FDA finds it needs to determine whether a 911(g)  
567 order is appropriate.

568

569 For example, FDA may request:

570

- 571 • Additional product analyses to verify information provided about specific  
572 components, ingredients, additives, or constituents present in the final product
- 573 • Data to support comparative claims, i.e., data comparing the tobacco product to a  
574 commercially available tobacco product that is representative of that type of  
575 tobacco product on the market (see, e.g., section 911(h)(2) of the FD&C Act)
- 576 • Samples of the tobacco product
- 577 • For products that have been on the market prior to the MRTPA submission, a  
578 summary of information that the manufacturer possesses regarding the product,  
579 including, but not limited to, adverse events from use of the product, levels of  
580 product use in the market, and consumer feedback regarding the product
- 581 • For products that have not been on the market prior to the MRTPA submission, a  
582 summary of any market research and information that was used to inform the  
583 development of the new product and its label, labeling and marketing plan

584

585 If you become aware of any new information relating to the effect of the proposed  
586 product on tobacco-related diseases and health-related conditions (including adverse  
587 events) while your application is pending with FDA, you should promptly provide this  
588 information to FDA.

589

590 Further, each applicant granted an order under section 911(g) must conduct postmarket  
591 surveillance and studies and annually submit the results of the surveillance and studies so  
592 FDA can assess, among other things, the impact of an order on consumer perception,  
593 behavior, and health. See sections 911(g)(2)(C) and (i)(1) of the FD&C Act. FDA asks

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594 the applicant to submit a plan for postmarket surveillance and studies. The plan should  
595 contain sufficient detail for FDA to evaluate whether the results from surveillance and  
596 studies will give FDA the information it needs to review the accuracy of the  
597 determinations on which it based the order. Section VII, “Postmarket Surveillance and  
598 Studies,” below, provides information and recommendations.

599 **C. Environmental Impact Considerations**

600  
601 FDA’s regulation implementing the National Environmental Policy Act (NEPA) of 1969  
602 requires that “[a]ll applications or petitions requesting agency action require the  
603 submission of an [environmental assessment] or a claim of categorical exclusion.” 21  
604 CFR 25.15(a).

605  
606 Currently there are no categorical exclusions in place for tobacco products; therefore, you  
607 must submit an environmental assessment as part of your MRTPA. You should refer to  
608 21 CFR Part 25 for additional information.

609 **VI. Scientific Studies and Analyses in MRTPAs**

610  
611 This section sets forth recommendations regarding scientific studies and analyses that  
612 should be contained in an MRTPA so that FDA can determine whether the criteria for  
613 issuance of an order under section 911(g) of the FD&C Act have been satisfied. FDA  
614 encourages anyone who is considering development of, or preparing an application for, a  
615 modified risk tobacco product to meet with FDA to discuss what studies would be  
616 appropriate for your product, so that you can best use your resources to conduct studies  
617 that will support your application.

618 **A. Key Areas of Investigation Regarding the Effect of an MRTP**

619  
620 In determining whether it can issue an order under section 911(g) of the FD&C Act for an  
621 MRTP, FDA must assess whether the applicant has demonstrated that the product will or  
622 is expected to benefit the health of individuals and the population as a whole. In order for  
623 an applicant to demonstrate that its product meets the criteria for issuance of an order  
624 under section 911(g) of the FD&C Act, the applicant’s MRTPA should address the  
625 following key areas of investigation:

- 626
- 627 • Health risks of the tobacco product;
  - 628 • The effect the tobacco product and its marketing may have on tobacco use  
629 behavior among current tobacco users;
  - 630 • The effect the tobacco product and its marketing may have on tobacco use  
631 initiation among non-users (both never users and former users);
  - 632 • The effect of the tobacco product’s marketing on consumer understanding and  
633 perceptions; and

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- 634       • The effect the tobacco product and its marketing may have on the population as a  
635       whole.

636               **1. Health Risks of the Tobacco Product**

637  
638       An MRTPA must provide scientific evidence regarding the effect of the product on the  
639       health of individuals so that FDA can determine whether the MRTP does, in fact, modify  
640       risk as claimed by the applicant and whether FDA can issue an order for such product  
641       under section 911(g) of the FD&C Act.

642  
643       In the case of an application for a risk modification order, the MRTPA must provide  
644       scientific evidence to demonstrate that the product significantly reduces harm and the risk  
645       of tobacco-related disease to individual users. See section 911(g)(1)(A) of the FD&C  
646       Act. In the case of an application for an exposure modification order, the MRTPA must  
647       provide scientific evidence to demonstrate that:

- 648  
649       • The magnitude of overall reductions in exposure to the substance or substances  
650       which are the subject of the application is substantial;  
651       • Such substance or substances are harmful;  
652       • Consumers actually use the product in a way that exposes them to the specified  
653       reduced level of the substance or substances;  
654       • Consumers are not exposed to higher levels of other harmful substances, or if they  
655       are, those increases are minimal, such that the reasonably likely overall impact of  
656       use of the product remains a substantial and measurable reduction in the overall  
657       morbidity and mortality among individual tobacco users; and  
658       • The scientific evidence that is available without conducting long-term  
659       epidemiological studies demonstrates that a measureable and substantial reduction  
660       in morbidity or mortality is reasonably likely in subsequent studies.

661  
662       See section 911(g)(2)(A)(iv) and (B)(i) & (ii) of the FD&C Act.

663  
664       FDA must also assess whether the tobacco product will benefit (see section 911(g)(1)(B)  
665       of the FD&C Act) or is expected to benefit (see section 911(g)(2)(B)(iv)) the health of  
666       the population as a whole before an order can be issued under section 911(g) of the  
667       FD&C Act. To make this determination, FDA must consider, among other things, the  
668       risks and benefits to all persons who may potentially use or be exposed to the tobacco  
669       product that is the subject of the application, including as compared to the use of products  
670       for smoking cessation approved to treat nicotine dependence. Section 911(g)(4) of the  
671       FD&C Act.

672  
673       In order to make the required demonstrations for issuance of an order, FDA recommends  
674       that applicants seeking either a risk modification order or an exposure modification order  
675       submit:  
676

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- 678
- 679
- 680
- 681
- 682
- 683
- 684
- Product analyses to validate information provided by the applicant regarding the formulation of the product as it relates to the risk or exposure modification;
  - Product analyses to assess users’ and non-users’ potential exposure to harmful substances; and
  - Human studies regarding actual use of the product to determine if users are likely to use the product in a manner that reduces their individual health risks or exposures as compared to using other commercially marketed tobacco products.

685 FDA also recommends that applicants seeking risk modification orders submit:

- 686
- 687
- 688
- 689
- Human studies that show the product’s use will result in a significant reduction in harm and the risk of tobacco-related disease to individual tobacco users.

690 FDA also recommends that applicants seeking exposure modification orders submit:

- 691
- 692
- 693
- 694
- 695
- 696
- 697
- 698
- 699
- 700
- 701
- 702
- Human studies that demonstrate that the level of exposure to harmful substances has been substantially reduced;
  - Nonclinical and/or human studies that demonstrate that the substance(s) or exposure(s) that have been reduced are harmful; and
  - Nonclinical and/or human studies that demonstrate that use of the product is expected to result in a measurable and substantial reduction in morbidity or mortality to individual tobacco users based on the effects of the product on an endpoint that is reasonably likely, based on epidemiological, therapeutic, pathophysiologic, or other evidence, to predict an effect on reducing harm or disease.

703 Scientific studies submitted by the applicant regarding the risk of the product should

704 enable FDA to fully assess – whether using clinical risk endpoints in the case of a risk

705 modification order or exposure risk endpoints in the case of an exposure modification

706 order - the health risks of the tobacco product as compared to other consumer behaviors,

707 including:

- 708
- 709
- 710
- 711
- 712
- 713
- 714
- 715
- 716
- 717
- 718
- 719
- 720
- The health risks associated with use of the product as compared to using other tobacco products on the market, including tobacco products within the same class of products;
  - The changes in health risks to users who switch from using another tobacco product to using the product, including tobacco products within the same class of products;
  - The health risks associated with switching to the product as compared to quitting the use of tobacco products;
  - The health risks associated with using the product in conjunction with other tobacco products;
  - The health risks associated with switching to the product as compared to using an FDA-approved tobacco cessation medication; and

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- 721       • The health risks associated with initiating use of the product as compared to never  
722       using tobacco products.  
723

724       Where a tobacco product presents novel features that may cause risks to non-users, you  
725       should also submit information regarding the health risks posed to non-users of the  
726       product.

727               **2.       Effect on Tobacco Use Behavior among Current Tobacco Users**  
728

729       In order for FDA to assess the full effect that an MRTP and its marketing may have on  
730       population health under section 911(g)(1)(B) or 911(g)(2)(B)(iv) of the FD&C Act, an  
731       MRTPA should contain scientific evidence about the effect the product may have on  
732       tobacco use behavior among current tobacco users. This includes consideration of areas  
733       such as the expected rates of use of the tobacco product by current tobacco users, the use  
734       of the tobacco product in conjunction with other tobacco products, and the potential for  
735       abuse and misuse of the product. An application must provide evidence regarding  
736       whether the product and its marketing will increase or decrease the likelihood that  
737       existing users of tobacco products who would otherwise stop using such products would  
738       instead switch to the tobacco product that is the subject of the application. See section  
739       911(g)(4)(B) of the FD&C Act.  
740

741       To address the effect on behavior among current tobacco users, FDA recommends that  
742       applicants submit:

- 743
- 744       • Nonclinical and/or human studies to assess the abuse liability and the potential for  
745       misuse of the product as compared to other tobacco products on the market;<sup>11</sup> and
  - 746       • Human studies regarding actual use of the product and consumer perception of the  
747       product, including its labeling, marketing and advertising.  
748

749       The scientific studies submitted by the applicant should inform FDA’s evaluation of the  
750       tobacco product’s impact on tobacco use behavior, including:

- 751
- 752       • The likelihood that current tobacco product users will start using the product;
  - 753       • The likelihood that tobacco users who adopt the product will switch to or switch  
754       back to other tobacco products that present higher levels of individual health risk;
  - 755       • The likelihood that consumers will use the product in conjunction with other  
756       tobacco products;

---

<sup>11</sup> Abuse liability is the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently.

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- 757       • The likelihood that users who may have otherwise quit using tobacco products  
758       will instead use the product; and  
759       • The likelihood that consumers will use the product as intended or designed.

760           **3.       Effect on Tobacco Use Initiation among Non-Users**

761  
762       A critical population health consideration under section 911(g)(1)(B) and  
763       911(g)(2)(B)(iv) of the FD&C Act is the effect that an MRTP and its marketing will have  
764       on tobacco use initiation among non-users (both never users and former users). An  
765       MRTPA must contain scientific evidence regarding the effect the product and its  
766       marketing will have on increasing the likelihood that persons who do not use tobacco  
767       products will start using the tobacco product that is the subject of the application. See  
768       section 911(g)(4)(C) of the FD&C Act.

769  
770       To address the effect of the MRTP on tobacco use initiation, FDA recommends that  
771       applicants submit:

- 772  
773       • Human studies that evaluate consumer perception of the product, including its  
774       labeling, marketing and advertising.

775  
776       These studies should be designed to provide evidence regarding the likelihood of  
777       population benefit or harm from the proposed product, including:

- 778  
779       • The likelihood that consumers who have never used tobacco products, particularly  
780       youth and young adults, will initiate use of the tobacco product;  
781       • The likelihood that non-users who adopt the tobacco product will switch to other  
782       tobacco products that present higher levels of individual health risk; and  
783       • The likelihood that former users of tobacco products will re-initiate use with the  
784       tobacco product.

785           **4.       Effect of Marketing on Consumer Understanding and Perceptions**

786  
787       Another important consideration is the effect that an MRTP and its marketing will have  
788       on consumer understanding and perceptions. All MRTPAs must contain evidence to  
789       show that the advertising and labeling concerning modified risk products enable the  
790       public to comprehend the information concerning modified risk and to understand the  
791       relative significance of such information in the context of total health and in relation to  
792       all of the diseases and health-related conditions associated with the use of tobacco  
793       products. See section 911(h)(1) of the FD&C Act.

794  
795       For exposure modification orders, any aspect of the product’s label, labeling, and  
796       advertising that would make it a modified risk tobacco product must be limited to an  
797       explicit or implicit representation that the product or its smoke does not contain or is free  
798       of a substance or contains or presents a reduced level of exposure to a substance. See  
799       section 911(g)(2)(A)(ii) of the FD&C Act. Applicants seeking an exposure modification

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800 order must demonstrate through testing of actual consumer perception that the proposed  
801 labeling and marketing of the product does not mislead consumers into believing that the  
802 product is or has been demonstrated to be less harmful, or mislead consumers into  
803 believing that the product presents less of a risk of disease than one or more other  
804 commercially marketed tobacco products. See section 911(g)(2)(B)(iii) of the FD&C  
805 Act.

806  
807 To address the effect of marketing on consumer understanding and perception, FDA  
808 recommends that applicants submit:

- 809  
810
  - Human studies regarding consumer understanding of the product, including its  
811 labeling, marketing and advertising.

812  
813 The scientific studies submitted by the applicant should inform FDA’s evaluation of the  
814 tobacco product’s marketing on consumer perception and understanding, including:

- 815  
816
  - The ability of consumers to understand the modified risk claims and the  
817 significance of the information in the context of one’s health;
  - 818 • Consumers’ beliefs about the health risks of using the product relative to other  
819 tobacco products, including those within the same class of products;
  - 820 • Consumer beliefs about the health risks of using the product relative to cessation  
821 aids; and
  - 822 • Consumer beliefs about the risks of using the product relative to quitting all  
823 tobacco use.

824 **5. Effect on the Population as a Whole**

825  
826 All applicants must demonstrate that the marketing of the tobacco product will or is  
827 expected to “benefit the health of the population as a whole.” See section 911(g)(1)(B)  
828 and 911(g)(2)(B)(iv) of the FD&C Act. Applicants seeking an exposure modification  
829 order must further demonstrate that issuance of an exposure modification order would be  
830 “appropriate to promote the public health.” Section 911(g)(2)(A)(i) of the FD&C Act.  
831 Therefore, an MRTPA should contain an overall assessment of the potential effect that  
832 the marketing of the product as proposed may have on tobacco-related morbidity and  
833 mortality in the population as a whole.

834  
835 To address the effect of an MRTP on the population as a whole, FDA recommends that  
836 applicants submit:

- 837  
838
  - Quantitative estimates of the effect the marketing of the product, as proposed,  
839 may have on the health of the population as a whole.

840  
841 The estimates should integrate all of the information regarding the marketing of the  
842 product and its potential effects on health, tobacco use behavior and tobacco use initiation  
843 to provide an overall assessment of the potential effect that the product’s introduction to



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844 the market may have on overall tobacco-related morbidity and mortality. FDA  
845 recommends that the applicant estimate the attributable risk of all of the various health  
846 effects for various types of individuals in the U.S. population, as well as the total number  
847 of individuals of each type. As an illustration, consider a product that an applicant  
848 maintains poses one-tenth of the risk of death from lung cancer as compared to smoking  
849 cigarettes. FDA recommends that the applicant quantify the potential changes in  
850 mortality to the various types of affected individuals in the U.S. population (see bullets  
851 below). This would include, among other things, an estimate of the number of smokers  
852 who are likely to switch to the product and the subsequent reduction in the number of  
853 lives lost due to tobacco use, the number of smokers who may use the product in  
854 conjunction with other tobacco products or instead of quitting and the subsequent effect  
855 on the number of lives lost due to tobacco use, as well as the number of non-smokers who  
856 may initiate use of tobacco with the product and the subsequent increase in the number of  
857 lives lost to tobacco use. FDA recommends that a similar approach be used to assess the  
858 potential impact on mortality resulting from other diseases, as well as morbidity in the  
859 various types of affected individuals in the U.S. population. The types of individuals  
860 may include, but are not limited to, the following:

- 861
- 862 • Tobacco users who switch from other commercially marketed tobacco
  - 863 products to the proposed product;
  - 864 • Tobacco users and non-users who, after adopting the proposed product, switch
  - 865 to or switch back to other tobacco products that may present higher levels of
  - 866 individual health risk;
  - 867 • Tobacco users who opt to use the proposed product rather than cease tobacco
  - 868 use altogether;
  - 869 • Tobacco users who opt to use the proposed product rather than an FDA-
  - 870 approved tobacco cessation medication;
  - 871 • Non-users who initiate tobacco use with the proposed product, such as youth,
  - 872 never users, former users;
  - 873 • Tobacco users who use the product in conjunction with other tobacco
  - 874 products; and
  - 875 • Non-users who experience health risks from the product.

876 **B. Detailed Considerations Regarding the Recommended Studies**  
877 **and Analyses**

878

879 Given the breadth of evidence needed to support the issuance of an order under section  
880 911(g) of the FD&C Act, it is unlikely that a single study will provide sufficient evidence  
881 to support FDA’s issuance of an order. Furthermore, it is unlikely that a set of studies of  
882 one type will provide sufficient evidence to support the issuance of an order. Therefore,  
883 as described above in section VI.A, FDA recommends that applicants provide  
884 information from a number of studies of different types in order to address the full range  
885 of areas of investigation set forth in section 911 of the FD&C Act so that FDA can  
886 determine whether or not it can issue an order under section 911(g) for the MRTP. These

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887 include product analyses, nonclinical studies, studies in adult human subjects, and  
888 secondary data analyses and modeling. Below is a more detailed description of the types  
889 of studies and analyses that FDA recommends an applicant use to address the key areas  
890 of investigation and recommendations for the conduct of these studies and analyses.

891  
892 In general, studies should be quantitative in nature<sup>12</sup> and designed in accordance with the  
893 principles outlined in section VI.C. The information that follows identifies the various  
894 outcomes these studies should assess when evaluating the impact of the tobacco product.

895 **1. Product Analyses**

896  
897 Product analyses regarding the chemistry and engineering of the product may be used to  
898 verify and validate the information submitted regarding the formulation of the product.  
899 In addition, product analyses will facilitate FDA’s understanding of the product, the  
900 potential for exposure to harmful or potentially harmful constituents from use of the  
901 product, and provide context for evaluating other data submitted in an MRTPA.

902  
903 For each product, FDA recommends that applicants conduct product analyses to  
904 determine levels of harmful and potentially harmful constituents (HPHC), including  
905 smoke constituents, as appropriate to the product.<sup>13</sup> Applicants should test for and report  
906 on the HPHC list as established by FDA under section 904(d) of the FD&C Act.<sup>14</sup>

907  
908 In testing your product for HPHCs, you should adhere to any rules or guidance FDA has  
909 issued in connection with section 904(a)(3) of the FD&C Act or, as applicable, under  
910 section 915. Absent rules or guidance to the contrary, for cigarettes, applicants should  
911 determine quantitative levels in smoke using both the ISO and Canadian Intense smoking  
912 regimens.<sup>15</sup> For other smoked tobacco products, applicants should determine quantitative  
913 levels in smoke using smoking regimens to reflect a wide range of smoking intensities  
914 that would be appropriate for the product. Applicants should justify the use of any  
915 alternative testing methods.

---

<sup>12</sup> The results of qualitative research, e.g., interviews and focus groups, may be submitted to provide insight about how consumers interact with the product or why consumers hold certain beliefs about a product. However, qualitative research alone is not sufficient and will not enable FDA to assess the effect that the product may have on the population.

<sup>13</sup> For a discussion of harmful and potentially harmful constituents, including smoke constituents, in tobacco products or tobacco smoke, see FDA’s Guidance for Industry and FDA Staff “*Harmful and Potentially Harmful Constituents*” in *Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act* (<http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM241352.pdf>).

<sup>14</sup> Further information about the list is available on the Internet (under the Regulatory Information heading) at <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm>.

<sup>15</sup> The ISO method is available at [http://www.iso.org/iso/iso\\_catalogue/catalogue\\_tc/catalogue\\_detail.htm?csnumber=28325&commid=52158](http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=28325&commid=52158). The Canadian method for measuring emissions from tobacco products is available in Part 3 of SOR 2000-273, available at <http://laws-lois.justice.gc.ca/PDF/SOR-2000-273.pdf>.

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916  
917 FDA recommends that applicants conduct product analyses on samples of the product  
918 manufactured on the same date and complete those analyses within a short timeframe.  
919 Where feasible, applicants should also provide data on multiple batches of product to  
920 provide evidence that product characteristics remain consistent across batches of  
921 production.

922 **2. Nonclinical Studies**

923  
924 Nonclinical studies include *in vitro*, *in vivo*, and *ex vivo* studies. The results of these  
925 studies may offer useful information about the health risks and abuse liability of a  
926 tobacco product. These studies may also provide context for data obtained from other  
927 types of studies, such as product analyses and human studies.

928  
929 FDA recommends that applicants conduct nonclinical studies to address the known  
930 clinical toxicities of tobacco products and evaluate a range of potential toxicities of the  
931 product as compared to other tobacco products on the market. Applicants should choose  
932 appropriate models for nonclinical studies that are sufficiently sensitive for the evaluation  
933 of the selected endpoint and be able to provide support for the model used, including an  
934 explanation of the sensitivity and probative value of the model chosen. For *in vivo*  
935 animal studies, researchers should administer the test product to animals by a route  
936 representative of human exposure, where feasible. Nonclinical toxicology studies should  
937 use methods that are sufficiently sensitive to assess the actual differences between use of  
938 the product and use of other tobacco products, or between use of the product and non-use  
939 of tobacco products.

940  
941 With respect to abuse liability, nonclinical studies should address differences in the abuse  
942 liability of the product compared to other tobacco products currently on the market. An  
943 assessment of abuse liability may rely on a battery of studies that could include animal  
944 models of conditioned place preference, drug discrimination and self-administration.

945 **3. Studies in Adult Human Subjects**

946  
947 Studies in human subjects (human studies) include clinical investigations,  
948 epidemiological studies, consumer perception studies, actual use studies and other studies  
949 that involve humans actually consuming or interacting with the product, its proposed  
950 labeling and/or marketing materials. Human studies provide FDA with information  
951 critical for determining what effect the product may have on the health of individuals and  
952 on the population as a whole if the product is commercially marketed as an MRTP.

953  
954 ***Health Risks and Tobacco Use Behavior***

955  
956 The types of human studies that can be conducted to evaluate the impact of a tobacco  
957 product on health risks and tobacco use behavior include experimental studies (e.g.,

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958 randomized clinical trials); observational epidemiological studies such as cross-sectional  
959 surveys, longitudinal surveys, case-controls studies, and cohort studies; and others.

960

961 FDA recommends that applicants conduct human studies to assess the full range of the  
962 human health risks related to the use of the tobacco product, including exposure to  
963 tobacco-related compounds (e.g., biomarkers of exposure) and health outcomes (e.g.,  
964 disease incidence or mortality), as well as tobacco use behaviors, including initiation of  
965 use of the tobacco product among never users and former users, rates that current tobacco  
966 users switch to the tobacco product, and patterns of use of the tobacco product by current  
967 tobacco users.

968

969 When conducting human studies in controlled settings, it is important to adhere to  
970 principles of good clinical practices, including adequate human subject protection.  
971 Further information on FDA regulations and available guidance documents on this topic  
972 can be accessed at

973 <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

974

975 When conducting observational epidemiological studies, applicants should take measures  
976 to reduce or prevent the occurrence of bias and to control for confounding factors, either  
977 by using an appropriate study design or applicable statistical methods during data  
978 analysis. The applicant should present information on the reliability and validity of  
979 measures used to assess the various outcomes.

980

981 *Actual use*

982

983 Actual use studies should allow consumers to interact freely with the product in real-  
984 world conditions. FDA recommends that these studies assess:

985

- 986 • How the product is consumed in early stages of use;
- 987 • How the product is consumed during continued use;
- 988 • The frequency and intensity (e.g., depth of inhalation) of product use;
- 989 • The amount of the product typically used per occasion;
- 990 • The duration of use per occasion;
- 991 • The use of the product with other tobacco products (i.e., the use of multiple  
992 tobacco products);
- 993 • The possible ways that a user may consume the product; specifically those  
994 that may differ from that intended by the applicant;
- 995 • The likelihood that a user may consume the product in a manner that may  
996 differ from that intended by the applicant;
- 997 • The potential impact to individual and public health from the failure to use the  
998 product as intended; and
- 999 • The elements of the product’s design and manufacture that may lend  
1000 themselves to product misuse by users.

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1002 *Human abuse liability*

1003

1004 FDA recommends that applicants conduct human abuse liability studies to assess the  
1005 impact of various features of the product on the speed and efficiency of nicotine delivery  
1006 and the formation of unprotonated nicotine. These features may include:

1007

- 1008 • The presence of pharmacologically active constituents (e.g., nicotine,  
1009 acetaldehyde, anabasine, and nornicotine);
- 1010 • Other ingredients in the product (e.g., buffering agents); and
- 1011 • Design features (e.g., tobacco cut size, use of reconstituted tobacco and/or filter  
1012 ventilation).

1013

1014 Human abuse liability studies should also assess the threshold dose(s) of nicotine for  
1015 producing reinforcing effects, discriminative stimulus effects, and physical dependence  
1016 (e.g., symptoms of withdrawal), accounting for variability of this dose across individuals.

1017

1018 *Consumer perception and understanding*

1019

1020 In order to assess how consumers perceive the product and its associated labels, labeling,  
1021 and/or marketing, FDA recommends that applicants conduct consumer perception  
1022 studies. These studies should provide data regarding how consumers perceive the risks to  
1023 health from using the product, and the likelihood of trying the product. Furthermore, the  
1024 applicant should provide data regarding consumer understanding of the product's  
1025 instructions for use and of the information concerning modified risk in the context of total  
1026 health. Applicants are encouraged to use methods that assess the impact of repeated  
1027 exposure to labels and advertising on consumer perceptions.

1028

1029 When designing consumer perception studies, applicants should take care that the studies  
1030 themselves do not promote use of the product, particularly among vulnerable populations,  
1031 such as youth, non-users of tobacco products, and pregnant women. FDA recommends  
1032 that applicants meet with FDA to discuss research plans before embarking on research  
1033 with vulnerable populations. Section IX.B of this guidance provides information on  
1034 requesting a meeting with FDA.

1035

1036 Applicants seeking exposure modification orders must also demonstrate that testing of  
1037 actual consumer perception shows that, as the applicant proposes to label and market the  
1038 product, consumers will not be misled into believing that the product is or has been  
1039 demonstrated to be less harmful, or presents or has been demonstrated to present less of a  
1040 risk of disease than one or more other commercially marketed tobacco products. See  
1041 section 911(g)(2)(B)(iii) of the FD&C Act. FDA acknowledges that there may be  
1042 challenges to constructing appropriate claim language that conveys the potential benefits  
1043 of the product to tobacco users and does not convey that the product is less harmful than  
1044 other tobacco products. As such, FDA recommends, when assessing consumer  
1045 perception of the product, labeling and/or marketing, that the applicant consider testing  
1046 several variations of the proposed claim(s) on labels and/or in advertisements. As

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1047 indicated previously, the applicant must provide FDA with the results of all studies, both  
1048 favorable and unfavorable, related to the product. Section 911(d)(5) of the FD&C Act.

1049 **4. Secondary Data Analyses and Computational Modeling**

1050  
1051 FDA acknowledges the difficulties inherent in making premarket assessments of the  
1052 effect that the introduction of a modified risk product would have on the population as a  
1053 whole and the public health. FDA encourages the development and application of  
1054 innovative analytical methods to make preliminary estimates of the potential effects of  
1055 some change in the marketplace. Methods for making similar estimates are commonly  
1056 used in the fields of economics, statistics, decision sciences, and demography, and  
1057 include secondary data analyses and computational modeling. Applicants may opt to use  
1058 currently available models in the scientific literature to forecast the harm to public health  
1059 from tobacco use. At this time, FDA does not endorse the use of any particular model.  
1060 Applicants may also opt to conduct secondary analyses of existing data to provide further  
1061 insight on the potential effects of modified risk products.

1062  
1063 When applying secondary data analyses and computational modeling techniques,  
1064 applicants should select appropriate techniques, use data from scientific analyses and  
1065 studies conducted in accordance with the general principles outlined below in section  
1066 VI.C, and conduct analyses of various scenarios, including worst-case scenarios.

1067 **C. General Principles for Scientific Studies and Analyses**

1068  
1069 This subsection describes sound scientific principles relating to the design and conduct of  
1070 studies to support submissions to FDA, including MRTPAs. Following these  
1071 recommendations will help to ensure that researchers and analysts conduct adequate and  
1072 well-designed studies.

1073  
1074 Applicants should conduct well-designed studies and analyses and provide sufficient  
1075 information about those studies and analyses to allow for critical evaluation and so that  
1076 other investigators could conduct similar studies and analyses to replicate the applicant's  
1077 findings. This will help provide adequate assurance that a finding in a study can be  
1078 replicated to show that the finding is not the result of unanticipated, undetected, or  
1079 systematic biases, study site or investigator-specific factors, or chance. It will also  
1080 provide a safeguard against instances in which the results of a study are the product of  
1081 fraudulent reporting of scientific studies because it allows for verification of study  
1082 results.

1083  
1084 Following these recommendations will also help FDA determine whether the results of an  
1085 analysis or study can be generalized from the study population under the conditions  
1086 tested to the population who will use the proposed modified risk tobacco product (e.g.,  
1087 broad segments of the U.S. population) under actual conditions of use.

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1089 FDA recommends that studies and analyses conducted to support an MRTPA have the  
1090 following characteristics:

1091

- 1092 • Clearly articulated objectives and hypotheses;
- 1093 • Protocols that employ standardized and validated methods of analysis;
- 1094 • Sample sizes that permit for robust statistical analyses;
- 1095 • Designs that permit valid comparisons with appropriate controls for the testing of  
1096 study hypotheses (selection of the control group(s) should be based on the  
1097 endpoint or effect to be evaluated<sup>16</sup>);
- 1098 • Procedures to minimize bias on the part of observers and analysts of the data and  
1099 prevent undue influences on the results and interpretation of the study data, such  
1100 as blinding, masking, random assignment to condition, etc.;
- 1101 • Procedures for the selection of human subjects to allow for generalizability of  
1102 study results to the U.S. population;
- 1103 • Methods for assigning subjects to different comparator groups that are appropriate  
1104 for making comparisons between groups with respect to pertinent variables;
- 1105 • Oversampling of populations that are particularly likely to be affected, positively  
1106 or negatively, by the marketing of the product;
- 1107 • Protocols that allow for conditions of use of the product that are reflective of how  
1108 the product will actually be used by consumers when it is marketed;
- 1109 • A study duration to allow for adequate assessment of selected endpoint(s) and/or  
1110 effects;<sup>17</sup> and
- 1111 • Analyses that adequately address the effects of the product on the study measures,  
1112 endpoints or outcomes.

1113

1114 In order to assure the quality and integrity of the data from studies and analyses relied on  
1115 or referenced in an MRTPA, the studies or analyses should, as applicable:

1116

- 1117 • Be conducted in laboratories accredited by a nationally or internationally  
1118 recognized external accreditation organization;
- 1119 • Use appropriate animal models and adhere to the best practices of refinement,  
1120 reduction, and replacement of animals in research and to applicable laws,  
1121 regulations, and policies governing animal testing, for example, the Animal  
1122 Welfare Act (7 U.S.C. 2131 et seq.) and the Public Health Service Policy of  
1123 Humane Care and Use of Laboratory Animals (available at  
1124 <http://grants.nih.gov/grants/olaw/references/phspol.htm>);

---

<sup>16</sup> For example, in a study designed to assess the effect of a modified risk tobacco product on disease risk compared to a commercially marketed tobacco product, it would be appropriate to include multiple comparator groups of both the product and the commercially marketed tobacco product based on tobacco use levels (e.g., smokers of less than 10 cigarettes per day, smokers of 10 or more cigarettes per day). In a study designed to assess the impact of a product's labeling on consumer perception of risk, the study may include comparator groups that view product labels that bear alternate versions of the proposed claim(s) or do not bear modified risk claims at all.

<sup>17</sup> For example, a study of the product's effect on cessation from tobacco use would likely require greater duration than a study to assess the topography of product use or consumer perception of the product.

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- 1125 • Implement good laboratory practices, for example, as specified in 21 CFR Part  
1126 58;
- 1127 • Be conducted by qualified and appropriately trained investigators;
- 1128 • Accurately account for and document the receipt, use, and disposition of all  
1129 investigational product(s);
- 1130 • Ensure the protection of human subjects by, for example:
  - 1131 ○ Implementing procedures for informed consent, such as those found in 21
  - 1132 CFR Part 50, and
  - 1133 ○ Ensuring study oversight by an Institutional Review Board, governed by
  - 1134 21 CFR Part 56.
- 1135 • Be conducted in accordance with study protocols and implementation procedures  
1136 that ensure that all study subjects receiving tobacco products are current daily  
1137 tobacco product users at least 21 years of age.

1138 **VII. Postmarket Surveillance and Studies**

1139  
1140 Each applicant who receives a risk modification or exposure modification order must  
1141 conduct postmarket surveillance and studies. See section 911(g)(2)(C)(ii) and (i)(1) of  
1142 the FD&C Act. For the purposes of implementing section 911 of the FD&C Act,  
1143 postmarket surveillance involves the identification and collection of unanticipated and  
1144 undesired events related to the tobacco product once it is introduced to the market;  
1145 postmarket studies generally are prospective, have well-defined study objectives and  
1146 require active recruitment compared to surveillance.<sup>18</sup>

1147  
1148 These postmarket surveillance and studies allow for evaluation of the effect of issuance of  
1149 an order on consumer perception, behavior, and health, and enable FDA to review the  
1150 accuracy of the determinations upon which the order was based. *Id.* An applicant who  
1151 receives a risk modification order must also conduct postmarket surveillance and studies  
1152 that provide information that FDA determines is otherwise necessary regarding the use or  
1153 health risks involving the tobacco product. See section 911(i)(1) of the FD&C Act.

1154  
1155 Applicants granted a risk modification order must submit protocols for required  
1156 postmarket surveillance for FDA concurrence within 30 days after receiving notice that  
1157 they are required to conduct such surveillance. Within 60 days of receipt of the protocol,  
1158 FDA must determine whether:  
1159

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<sup>18</sup> We recognize that section 505(o) of the FD&C Act regarding postmarket review of new drugs and the related guidance document (see *Guidance for Industry Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>) make distinctions between the postmarket studies and postmarket clinical trials. No such distinctions are made in section 911 of the FD&C Act and we do not make such distinctions in this guidance.



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- 1160 • The principal investigator responsible for the surveillance has sufficient  
1161 qualifications and experience to conduct such surveillance; and
- 1162 • The protocol will result in collection of the data or other information FDA  
1163 determines is necessary to protect the public health, including data and  
1164 information that the MRTP continues to satisfy the requirements for the issuance  
1165 of an order under section 911(g)(1).  
1166

1167 Applicants who receive an exposure modification order must agree to conduct postmarket  
1168 surveillance and studies in accordance with a protocol approved by FDA. See section  
1169 911(g)(2)(C)(ii) of the FD&C Act. FDA recommends that these applicants follow the  
1170 same timelines that apply to the approval of protocols relating to risk modification orders.  
1171

1172 All applicants must submit the results of postmarket surveillance and studies annually.  
1173 See sections 911(g)(2)(C)(iii) and 911(i)(1). Failure to conduct or submit the required  
1174 postmarket surveillance and studies is a basis for withdrawal of an applicant’s order. See  
1175 section 911(j)(4) of the FD&C Act. Furthermore, any applicant who fails to conduct or  
1176 submit the required postmarket surveillance and studies would be liable for civil  
1177 monetary penalties under section 303(f)(9)(B)(ii) of the FD&C Act (21 U.S.C.  
1178 333(f)(9)(B)(ii)), and may be subject to other regulatory and enforcement action by FDA.  
1179

1180 In order to ensure that applicants are prepared to satisfy the post-market review  
1181 requirements in section 911 of the FD&C Act, FDA encourages applicants to submit with  
1182 their MRTPAs draft protocols and/or detailed outlines of the postmarket surveillance and  
1183 studies they plan to conduct. FDA will review and comment on these materials and work  
1184 with applicants in developing appropriate protocols during the MRTPA review process so  
1185 that a final version of the protocols can be timely completed and approved if an order  
1186 under section 911(g) is issued.

1187 **A. Postmarket Surveillance**  
1188

1189 In order to grant a risk modification or exposure modification order, the Agency must  
1190 have sufficient evidence at the time of issuance of the order that marketing of the MRTP  
1191 will or is expected to benefit the health of individuals and of the population as a whole,  
1192 taking into account both users and non-users of tobacco products. See section  
1193 911(g)(1)(B) and (g)(2)(B)(iv) of the FD&C Act. The knowledge related to the effect of  
1194 the MRTP on individuals and the population as a whole can change over time due to a  
1195 variety of factors, including changes in tobacco use behavior, consumer perceptions, and  
1196 changes in the tobacco product marketplace. During the postmarket period, the MRTP  
1197 will be used in settings different from studies in human subjects conducted during the  
1198 development of the MRTP, and a much larger population may be exposed to the product  
1199 for a much longer term. Therefore, postmarket surveillance is a very important tool for  
1200 monitoring the effects of the MRTP on individual and population health.  
1201

1202 For the purposes of this draft guidance, we identify two types of postmarket surveillance:  
1203

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- 1205
- 1206
- 1207
- 1208
- 1209
- Passive surveillance, which relies on spontaneous reports submitted by tobacco product manufacturers, health care professionals, or consumers; and
  - Active surveillance, which relies on an active collection of data. Data may be collected by local agencies (e.g., city, state, American Indian tribal) or through registries established by tobacco product manufacturers, published literature or other sources.

1210 **B. Postmarket Studies**

1211

1212 The objective of conducting postmarket studies is to gather and assess information about  
1213 the product after introduction into the marketplace, including but not limited to:

1214

- 1215
- 1216
- 1217
- 1218
- 1219
- 1220
- Data on real world use of the MRTP in a general population of tobacco users;
  - Tobacco-related adverse events;
  - Longer-term assessment of exposure and health outcomes, including intermediate clinical outcomes and mortality; and
  - Ongoing assessment of consumer perception and tobacco use behavior (e.g., initiation, cessation, frequency of use).

1221 **C. Outcomes Evaluated in Postmarket Surveillance and Studies**

1222

1223 The outcomes evaluated in postmarket surveillance and studies should focus on the effect  
1224 of the MRTP on consumer perception, behavior and health under real world conditions of  
1225 use.

1226

1227 Postmarket surveillance and studies of consumer perception should provide data  
1228 regarding how consumers perceive the risks to health from using the marketed product,  
1229 and the likelihood they will try the product. These studies should also provide  
1230 information concerning consumers' understanding of the marketed product's instructions  
1231 for use and its modified risk claims.

1232

1233 Postmarket surveillance and studies of consumer behavior should provide data with  
1234 respect to the effect the product's marketing has on whether current tobacco users switch  
1235 to the product from their usual product, whether current tobacco users continue using the  
1236 product, whether current tobacco users who would otherwise cease all tobacco use switch  
1237 to the product instead, and whether non-users start using the product.

1238

1239 Postmarket surveillance and studies of consumer health should provide data with respect  
1240 to the health risks of the MRTP, including the effect the product has on tobacco-related  
1241 morbidity and mortality. Surveillance and studies should measure the health risks to  
1242 individuals from using the product as compared to using other tobacco products or  
1243 quitting use of tobacco products. Specific health outcomes to consider may include, but  
1244 are not limited to:

1245

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- New diagnosis or worsening diagnosis by health care providers of particular disease risks that may be associated with the use of the MRTP, including the risk of development of cancers, stroke, cardiovascular diseases, non-malignant respiratory diseases, fetal toxicity, oral/dental diseases, etc.
  - Occurrence of emergency room visits or hospitalizations for illnesses associated with the use of the MRTP (e.g., rate of hospitalization and the proportion of subjects with hospitalizations for tobacco-related illness).
  - Physiologic or blood chemistry parameters of MRTP users such as HPHC levels, measures of biomarkers of exposure, measures of biomarkers of disease, ECG, and pulmonary function testing.

1256

1257 *Adverse Events*<sup>19</sup>

1258

1259 An important component of postmarket surveillance and studies is to collect information  
1260 on adverse events that occur in relation to a product. For purposes of this draft guidance,  
1261 an adverse event (AE) is any health-related event associated with the use of a tobacco  
1262 product in humans that is adverse or unfavorable, whether or not it is considered tobacco-  
1263 product related.<sup>20</sup> An AE can arise from any use of the product (including use in  
1264 combination with other products and overdose).

1265

1266 Postmarket surveillance and studies should identify adverse events and provide data on  
1267 their nature, frequency, and potential risk factors so that informed decisions on risk  
1268 minimization can be made. A serious AE is an AE that results in any of the following:

1269

- Death;
- A life-threatening condition or event;
- Persistent or substantial disability or incapacitation;
- Hospitalization or prolonged hospitalization; or
- A congenital anomaly or birth defect.

1275

1276 You should report all adverse events that occur during surveillance or while monitoring  
1277 studies. Non-serious AEs should be reported as part of your annual submission of the  
1278 results of postmarket studies and surveillance. FDA requests that serious AEs be  
1279 reported to CTP's Office of Science within 15 business days after the report is received  
1280 by the applicant.

1281 **D. Design of Postmarket Studies and Active Surveillance**

1282

1283 Depending on the study objectives, the study design used for postmarket studies could  
1284 include observational epidemiological studies, interventional studies, such as randomized

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<sup>19</sup> Section 909(a) of the FD&C Act directs FDA to issue regulations requiring the reporting of adverse events for tobacco products. FDA has not yet issued such regulations.

<sup>20</sup> Your submission will not be construed by FDA as an admission that the tobacco product involved caused or contributed to the adverse event being reported. See section 756 of the FD&C Act (21 U.S.C. 379v).

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1285 clinical trials, or studies of other design. For all studies and active surveillance, the draft  
1286 protocol or the outline submitted to FDA with your MRTPA should include the following  
1287 elements:

- 1288
- 1289 • Objective(s);
- 1290 • Hypotheses;
- 1291 • Background information (e.g., a critical review of the literature, brief description  
1292 of the new tobacco product and any regulatory history, the significance of the  
1293 study to be conducted);
- 1294 • Design and setting (e.g., clinic, community) of the study;
- 1295 • Sample size and power calculation (please specify strata and clustering as  
1296 appropriate);
- 1297 • Relative standard errors for subgroups (if appropriate);
- 1298 • Study population (selection of study population, number of subjects to be  
1299 enrolled, inclusion/exclusion criteria, comparison group(s));
- 1300 • Primary and secondary endpoints (definition and success criteria);
- 1301 • Statistical analysis plan (description of the statistical methods to be employed, the  
1302 reason for your choice of sample size, including calculations of the power of each  
1303 study, and the level of significance and/or confidence level to be used);
- 1304 • Data collection procedures and instruments;
- 1305 • Baseline and follow-up assessments and duration of follow-up;
- 1306 • Case report forms;
- 1307 • Documentation describing steps to be taken to ensure the protection of human  
1308 subjects, for example, proposed informed consent and IRB approval forms; and
- 1309 • Study milestone and timeline elements, including study initiation, annual  
1310 enrollment goals, completion of enrollment, completion of follow-up, and  
1311 submission of final report.

## 1312 **VIII. Submission Information**

### 1313 **A. Organizing Your MRTPA for Submission to FDA**

1314  
1315 You should organize your MRTPA into the following distinct sections:

#### 1316 **1. Cover Letter**

1317  
1318 The cover letter should contain:

- 1319
- 1320 • The name and address of your company;
- 1321 • An authorized contact's name, title, address, phone number, fax number, and  
1322 email address;
- 1323 • The brand name and, if applicable, subbrand name of the proposed modified  
1324 risk tobacco product;

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- 1344
- The name of the manufacturer;
  - A list of all previous submissions to CTP for the proposed MRTP product or any product that is the same except for the claims that are the subject of your application, e.g., a submission of listing of ingredients in tobacco products submitted pursuant to section 904 of the FD&C Act, a substantial equivalence report, a request for an exemption from substantial equivalence, or a premarket tobacco product application, or a previous MRTPA, and what action FDA took as a result of any such submission;
  - A statement regarding how you have satisfied, or intend to satisfy, any applicable premarket review requirements under section 910 of the FD&C Act;
  - A list of dates of any prior meetings with FDA about the tobacco product that is the subject of the MRTPA;
  - A statement whether you are seeking a risk modification order or an exposure modification order; and
  - A description or listing of the specific portions of the application you believe constitute trade secret or confidential commercial information that is exempt from disclosure. In the alternative, you may submit a second version of the application with transparent highlights of proposed redactions. (See section X, Confidentiality, for more information).

1345           **2.       Table of Contents and Summary**

1346

1347       A comprehensive table of contents should precede a summary of the application and all

1348       other sections of the application.

1349

1350       The application should contain a summary of the application in enough detail that the

1351       reader may gain a good general understanding of the data and information in the

1352       application, including the quantitative aspects of the data. The summary should discuss

1353       all aspects of the application, and synthesize the information into a well-structured and

1354       unified document. The summary should be written at approximately the level of detail

1355       required for publication in, and meet the editorial standards generally applied by,

1356       refereed scientific journals. To the extent possible, data in the summary should be

1357       presented in tabular and graphic forms. The summary should contain the following

1358       information:

- 1359
- 1360
- 1361
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- 1363
- 1364
- 1365
- 1366
- 1367
- The proposed modified risk claims;
  - A statement briefly describing the type of tobacco product and providing the scientific rationale for the potential benefits of the tobacco product;
  - A summary of the information and scientific data submitted in the application; and
  - A concluding discussion describing how you have met each of the relevant statutory requirements for the type of order you are seeking under section 911(g) of the FD&C Act.

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1368           **3.       Descriptive Information**

1369

1370       The application should contain a section that includes the following descriptive  
1371       subsections:

1372

- 1373           • A subsection describing the proposed product;
- 1374           • A subsection describing the formulation of the product;
- 1375           • A subsection describing the conditions for using the product; and
- 1376           • A subsection describing how consumers actually use the product.<sup>21</sup>

1377

1378       See section V for guidance about the information that should be contained in each of  
1379       these descriptive subsections.

1380           **4.       Labels, Labeling and Advertising**

1381

1382       The application should contain a section describing how the applicant intends to  
1383       communicate the proposed modified risk claim(s) to the public and including copies of  
1384       proposed advertising and labeling and sample product labels and labeling as described  
1385       above in section V.A.1 and 4.

1386           **5.       Environmental Impact**

1387

1388       The application should contain an environmental assessment under 21 CFR Part 25.

1389           **6.       Summary of All Research Findings**

1390

1391       The application should contain a section summarizing all of the research findings related  
1392       to the product, both favorable and unfavorable. FDA recommends that this portion of the  
1393       application be organized according to the key areas described in section VI.A:

1394

- 1395           • *Health Risks of the Tobacco Product.*
- 1396           • *Effect on Tobacco Use Behavior among Current Users.*
- 1397           • *Effect on Tobacco Use Initiation among Non-Users.*
- 1398           • *Effect of Marketing on Consumer Understanding and Perceptions.*
- 1399           • *Effect on the Population as a Whole.*

1400

1401       We also recommend that applicants include a tabulated index of all studies and analyses  
1402       organized by the key areas above. This index should also be organized by study type  
1403       (product analyses, nonclinical studies, studies in adult human subjects, secondary data  
1404       analyses and modeling) and identify each study and analysis by name, section and page  
1405       numbers. For electronic submissions, the index should also include a hypertext link to

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<sup>21</sup> Findings from actual use studies should be submitted as part of your summary of all research findings.

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1406 each study and analysis. If any of the documents provided appear in peer-reviewed  
1407 literature, please provide a citation.

1408 **7. Scientific Studies and Analyses**

1409  
1410 This section should include the documents relating to the research referenced elsewhere  
1411 in the MRTPA as well as any other documents related to research findings conducted,  
1412 supported, or possessed by the tobacco product manufacturer. See section V.A.5. To  
1413 facilitate review, the documents relating to research findings should be complete and  
1414 well-organized.

1415  
1416 Applicants should organize studies by study type (i.e., product analyses, non-clinical  
1417 studies, human studies, and secondary analyses and modeling) and follow the submission  
1418 recommendations below for each study type.

1419  
1420 ***Product Analyses***

1421  
1422 FDA recommends reporting HPHC information in a tabular format using separate  
1423 columns, in the order listed below (from left to right) for each of the following:  
1424

- 1425 • The constituent name;
- 1426 • The constituent's common name(s);
- 1427 • The corresponding Chemical Abstract Services (CAS) number;
- 1428 • The unit of measure;
- 1429 • The level measured for the proposed product (with 95% confidence intervals);
- 1430 • The sample size; and
- 1431 • The method of measuring and reference quotes.

1432  
1433 FDA recommends separate tables for results generated using the ISO and Canadian  
1434 Intense smoking regimens, when applicable. Documentation of laboratory accreditation  
1435 should be included in the MRTPA.

1436  
1437 FDA recommends reporting information related to other product features (e.g., total  
1438 particulate matter, packaging, shelf life, etc.) as follows:

- 1439
- 1440 • Mean level measured for the product (with 95% confidence intervals);
- 1441 • Unit of measure;
- 1442 • Sample size;
- 1443 • Test method, linked to method defined within design specifications;
- 1444 • Test date and location; and
- 1445 • Product lot number or the date of manufacture.

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1447 *Nonclinical and Human Studies*

1448

1449 For individual study reports, the applicant should submit descriptions of:

1450

- The study objective;

1451

- The hypotheses tested;

1452

- The study design;

1453

- The study population, animals, bacteria strain, or cell line; including sample size, and comparator groups;

1454

1455

- The methods of data collection and analysis; and

1456

- The findings, key limitations, and conclusions.

1457

1458 In addition, the following information should be included, where applicable:

1459

- The original study protocol(s) used;

1460

- Any amendments (which should be dated) to the study protocol;

1461

- The final study protocol;

1462

- A justification for the method selected, i.e. appropriateness for the evaluation of the selected endpoint;

1463

1464

- All raw data and data files used to generate the results;

1465

- The questionnaires used;

1466

- Any transcripts or recordings of interviews and focus groups, where applicable;

1467

1468

- Case report forms;

1469

- For nonclinical studies, documentation describing the actions taken to ensure reliability and validity of the study (for example, documentation of good laboratory practices as specified in 21 CFR Part 58);

1470

1471

1472

- Documentation describing the actions taken to ensure the protection of human subjects (for example, documentation of study oversight by a qualified Institutional Review Board duly constituted and operating under 21 CFR Part 56, and documentation of informed consent procedures such as those described in 21 CFR Part 50);

1473

1474

1475

1476

1477

- A detailed description of the statistical analyses employed, including all variables, confounders, and subgroup analyses, and a full report of the findings;

1478

1479

1480

- Information on Data Monitoring Committee members;

1481

- Information on any contract research organization if obligations were transferred for the conduct of any study; and

1482

1483

- Investigator expertise and credentials.

1484

1485

1486 For each study, the report should also identify whether the study was conducted by or on  
1487 the applicant's behalf.

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1489                    ***Secondary Data Analyses and Modeling***

1490

1491        For other analyses and modeling, the applicant should provide:

1492

- 1493                    • Explanations and justification of the technique used;
- 1494                    • Assumptions used in the development of any models and parameters;
- 1495                    • A listing of the parameters used in the analyses and/or models;
- 1496                    • Data used to derive parameters or estimates and a rationale for the
- 1497                           applicability of the data for the given parameter; and
- 1498                    • The results of various scenarios, including worst-case scenarios.

1499

1500        Applicants should also address the inherent uncertainty in these approaches as they

1501        discuss the results derived from available secondary data and use of computational

1502        models.

1503        **B.     Single Application**

1504

1505        Section 911(l)(4) of the FD&C Act requires FDA to permit the filing of a single

1506        application for any tobacco product that is a new tobacco product under section 910 of

1507        the FD&C Act and which the applicant seeks to commercially market with modified risk

1508        claims. Accordingly, if the tobacco product for which you are seeking an order under

1509        section 911(g) of the FD&C Act is a new tobacco product for which you must also satisfy

1510        applicable premarket review requirements under section 910 of the FD&C Act, you may

1511        file a single application. The single application must include the information required for

1512        the applicable premarket review (i.e., a substantial equivalence report, request for

1513        exemption from substantial equivalence requirements, or the information required for

1514        premarket review under section 910(b) of the FD&C Act), as well as the information

1515        required to support issuance of an order under section 911(g) of the FD&C Act.

1516

1517        If you file a single application, it should be organized as follows:

1518

- 1519                    • Cover letter. The cover letter should include:
  - 1520                    ○ Identification of the submission as a single application permitted under
  - 1521                           section 911(l)(4) of the FD&C Act;
  - 1522                    ○ The name and address of your company;
  - 1523                    ○ An authorized contact’s name, title, address, phone number, fax number,
  - 1524                           and email address;
  - 1525                    ○ The brand name and, if applicable, subbrand name of the tobacco product;
  - 1526                    ○ The name of the manufacturer;
  - 1527                    ○ A list of all previous submissions to CTP for the proposed MRTP product
  - 1528                           or any product that is the same except for the claims that are the subject of
  - 1529                           your application, e.g., a submission of listing of ingredients in tobacco
  - 1530                           products submitted pursuant to section 904 of the FD&C Act or a previous
  - 1531                           MRTPA, and what action FDA took as a result of any such submission;

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- 1532           ○ A statement regarding what type of premarket review you are seeking (a  
1533           substantial equivalence determination, an exemption from substantial  
1534           equivalence requirements, or a marketing authorization order under  
1535           section 910(c)(1)((A)(i));
- 1536           ○ A list of dates of any prior meetings with FDA about the tobacco product  
1537           that is the subject of the MRTPA;
- 1538           ○ A statement whether you are seeking a risk modification order or an  
1539           exposure modification order; and
- 1540           ○ A description or listing of the specific portions of the application you  
1541           believe constitute trade secret or confidential commercial information that  
1542           is exempt from disclosure. In the alternative, you may submit a second  
1543           version of the application with transparent highlights of proposed  
1544           redactions. (See section X, Confidentiality, for more information).
- 1545           • Premarket review information. Your application must contain all the information  
1546           required for a substantial equivalence report, request for exemption from  
1547           substantial equivalence requirements, or for premarket review under section  
1548           910(b) of the FD&C Act. For details on how to submit a substantial equivalence  
1549           report under section 905(j) (21 U.S.C. 387e(j)), see FDA’s Guidance for Industry  
1550           *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco*  
1551           *Products* and FDA’s Draft Guidance for Industry *Demonstrating the Substantial*  
1552           *Equivalence of a New Tobacco Product: Responses to Frequently Asked*  
1553           *Questions*. For details on how to request exemptions from the substantial  
1554           evidence requirements, see FDA’s final rule – *Exemptions from Substantial*  
1555           *Equivalence Requirements for Tobacco Products* (76 FR 38961; July 5, 2011).  
1556           For details on how to submit a Premarket Tobacco Product Application (PMTA)  
1557           under section 910(b) (21 U.S.C. 387j(b)), see FDA’s Draft Guidance for Industry  
1558           *Applications for Premarket Review of New Tobacco Products*.
- 1559           • Modified risk information. Your application must also contain all the information  
1560           required for issuance of a modified risk order under section 911(g) of the FD&C  
1561           Act. To the extent data or information contained in the premarket review portion  
1562           of the application is also relevant to or required for the modified risk  
1563           determination, you may cross-reference that data or information rather than  
1564           duplicating it in the modified risk portion of the application.

1565   **C.    How and Where Should I Submit My MRTPA?**

1566  
1567   In order to ensure the accessibility of documents and facilitate more effective and  
1568   efficient communication between you and FDA regarding your submission, FDA  
1569   recommends that you do the following:

- 1570
- 1571           • Uniquely number all pages of your submission using continuous pagination;
  - 1572           • Provide English translations for any foreign language documents. Applicants  
1573           should also provide the original foreign language document and certification that  
1574           the translation into English is accurate; and

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- 1575           • Create and submit a glossary or explanation of any abbreviations, acronyms, or  
1576           industry-specific terminology or codes.

1577  
1578       There are three ways to submit your MRTPA:

- 1579  
1580  
1581           • Electronic format submitted via the FDA Electronic Submission Gateway;  
1582           • Electronic format submitted on physical media (e.g., CD or DVD); or  
1583           • Paper format.

1584  
1585       FDA strongly encourages you to submit your MRTPA in an electronic format to  
1586       facilitate efficiency and timeliness of data submission and processing. You can securely  
1587       submit your application via the FDA Electronic Submissions Gateway (ESG). To  
1588       prepare for this capability, please refer to the ESG website instructions for setting up a  
1589       WebTrader account at

1590       <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm114831.htm>.

1591  
1592       MRTPAs submitted in paper or on electronic media should be sent to:

1593           Food and Drug Administration  
1594           Center for Tobacco Products  
1595           Document Control Center  
1596           Building 71, Room G335  
1597           10903 New Hampshire Avenue  
1598           Silver Spring, MD 20993-0002

1599  
1600           ***Physical Electronic Media***

1601  
1602       Files submitted on electronic media should be stored on a CD/DVD or flash drive media.  
1603       Electronic media should be labeled with your company name, a contact phone number,  
1604       “Modified Risk Tobacco Product Application - *name of proposed modified risk tobacco*  
1605       *product*,” submission date, and series number (e.g., “disc 1 of 2”). The files should  
1606       include a signed cover letter prominently identified as a “Modified Risk Tobacco Product  
1607       Application,” and should also identify the software (name, version, and company) that  
1608       you used to confirm the submission is free of viruses or other malware. In case we have  
1609       difficulty accessing the digital media, we recommend that you also include a paper copy  
1610       of the cover letter that prominently identifies the submission as a “Modified Risk  
1611       Tobacco Product Application – *name of proposed modified risk tobacco product*” and  
1612       includes the manufacturer’s name, address and phone number.

1613           ***Electronic Submission Formats***

1614  
1615       For MRTPAs submitted in electronic format, we recommend that all content (including  
1616       the cover letter), except raw data, be in Portable Document Format (PDF) files  
1617       compatible with Adobe Acrobat 6.0 or higher. Files should not be password protected or  
1618       encrypted. In preparing your submission in PDF format, we recommend that you:

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- Create PDF files directly from an electronic source such as a word processing file or excel;
  - Avoid image-only based PDF files whenever possible because scanned images are more difficult to read and search. If you scan a document to create a PDF file, we recommend that you capture text by optical character recognition (OCR) software so that the text of the resulting electronic documents is reasonably accessible and searchable;
  - Create a submission table of contents and format it using bookmarks designed to help the reader navigate through the document efficiently.
- 1626
- 1627

Any raw data submitted with an MRTPA should be submitted in an electronic source file format such as Microsoft Excel or SAS transport file.

1628

1629

1630

1631

**D. What Happens After You Submit an MRTPA?**

1632 FDA will first conduct an administrative review of your MRTPA for completeness.  
1633 Applicants should prepare complete, high quality submissions that facilitate FDA’s  
1634 complete and timely review. If FDA finds that your MRTPA does not contain  
1635 information required by section 911 of the FD&C Act for a risk modification order or  
1636 exposure modification order,<sup>22</sup> FDA may refuse to file your application.

1637

1638 FDA may request additional information to clarify issues, ask questions that arise during  
1639 the review process, and ask for updates on ongoing studies.

1640

1641 As required by section 911(f) of the FD&C Act, FDA will refer your application to the  
1642 Tobacco Products Scientific Advisory Committee (TPSAC) and ask TPSAC to report its  
1643 recommendations on the application to FDA within 60 days. FDA will also make the  
1644 application available to the public (except for matters in the application that are trade  
1645 secrets or otherwise confidential commercial information) and request comments  
1646 pursuant to section 911(e) of the FD&C Act. FDA intends to make the application  
available to the public through FDA’s Center for Tobacco Products’ website:  
1647 <http://www.fda.gov/TobaccoProducts/default.htm>.

1648

1649

1650

**E. Can I Withdraw My Pending MRTPA?**

1651 You may withdraw your pending MRTPA at any time. You should promptly notify FDA  
1652 in writing of your decision to withdraw your application. Withdrawal of an MRTPA  
1653 does not prevent you from submitting a subsequent MRTPA for the same tobacco  
1654 product in the future. However, any subsequent MRTPA should be complete without  
referencing data or any other information in the original MRTPA. FDA intends to act  
upon any subsequent MRTPA no later than 360 days after its receipt.

---

<sup>22</sup> For example, FDA may refuse to file your application if you do not provide sample product labels and labeling required by section 911(d)(4), or for an exposure modification order, you do not provide results from testing of actual consumer perception required by section 911(g)(2)(b)(iii).

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1655 **F. What is FDA’s Timeframe for Review of an MRTPA?**

1656

1657 FDA intends to act upon your MRTPA no later than 360 days after the receipt of an  
1658 application that contains the information required by section 911 of the FD&C Act.<sup>23</sup>

1659

1660 Similarly, if you choose to file a single application seeking authorization to market your  
1661 new tobacco product under section 910 of the FD&C Act and an order under section  
1662 911(g) of the FD&C Act, FDA intends to act upon your single application no later than  
1663 360 days after its receipt.

1664 **G. What Happens After an Order Under Section 911(g) of the FD&C**  
1665 **Act is Issued?**

1666

1667 An applicant granted an order under section 911(g) of the FD&C Act may commercially  
1668 market the tobacco product as described in the order issued by FDA. Note that an order  
1669 under section 911(g) is issued for specific modified risk claims. Introducing or delivering  
1670 for introduction into interstate commerce a tobacco product the label, labeling, or  
1671 advertising of which makes modified risk claims other than those described in the  
1672 product’s order is a violation of section 911 of the FD&C Act.

1673

1674 Furthermore, the 911(g) order is issued for the product that is the subject of the MRTPA.  
1675 Introducing or delivering for introduction into interstate commerce a tobacco product  
1676 other than that described in an order issued under section 911(g) of the FD&C Act may  
1677 cause the tobacco product to be in violation of section 911 of the FD&C Act. If an  
1678 applicant makes changes to the product that would trigger the premarket requirements of  
1679 section 905(j) or 910 of the FD&C Act,<sup>24</sup> the applicant must (in addition to satisfying any  
1680 applicable premarket review requirements under section 910 of the FD&C Act) submit an  
1681 MRTPA and FDA must issue an order under section 911(g) of the FD&C Act for the new  
1682 tobacco product. Note that FDA’s Guidances for Industry *Section 905(j) Reports:*  
1683 *Demonstrating Substantial Equivalence for Tobacco Product* and *Demonstrating the*  
1684 *Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked*  
1685 *Questions* describe changes that can be made to tobacco products for which FDA does not  
1686 intend to enforce the premarket review requirements of section 905(j) and 910 of the  
1687 FD&C Act. In such situations, FDA also does not intend to enforce the premarket review  
1688 requirements of section 911.

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<sup>23</sup> For additional information regarding timing of FDA’s review of MRTPAs refer to FDA’s Draft Guidance for Industry, *Preliminary Timetable for the Review of Applications for Modified Risk Tobacco Products under the Federal Food, Drug, and Cosmetic Act* (<http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM191915.pdf>).

<sup>24</sup> FDA’s Guidance for Industry *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products* and FDA’s Draft Guidance for Industry *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions* provide further guidance on the changes to a tobacco product that make it a “new tobacco product.”

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1689 **H. Can FDA Withdraw an Order Issued Under Section 911(g)?**

1690

1691 Yes. The grounds for withdrawal of an order issued under section 911(g) are set forth in  
1692 section 911(j) of the FD&C Act.

1693 **I. Can I Renew an Order Issued Under Section 911(g)?**

1694

1695 An exposure modification order issued under section 911(g)(2) of the FD&C Act will be  
1696 effective for a term of not more than 5 years. FDA may renew an exposure modification  
1697 order if the applicant files a new application and FDA finds that the requirements for  
1698 such order under section 911(g)(2) continue to be satisfied. Section 911(g)(2)(C)(i) of  
1699 the FD&C Act.

1700

1701 A risk modification order issued under section 911(g)(1) of FD&C Act will be effective  
1702 for the period of time specified in the order issued by FDA. Section 911(h)(4) of the  
1703 FD&C Act. FDA may renew a risk modification order if the applicant files a new  
1704 application and FDA finds that the requirements for such order under section 911(g)(1)  
1705 continue to be satisfied.

1706

1707 When submitting an application for renewal of an order issued under section 911(g), you  
1708 should ensure that you have complied with applicable requirements to provide results  
1709 from the required postmarket surveillance and studies conducted pursuant to your order.  
1710 Section 911(g)(2)(C)(iii) and 911(i)(1) of the FD&C Act. You should also submit with  
1711 your application any updated study results from and all data collected in the required  
1712 postmarket surveillance and studies. See section 911(l)(1)(E) and 911(d)(5) of the FD&C  
1713 Act.

1714 **IX. Investigational Use of Tobacco Products**

1715 **A. Exemptions for Investigational Use of Tobacco Products**

1716

1717 You must file an MRTPA and obtain an order from FDA under section 911(g) of the  
1718 FD&C Act before you can introduce or deliver for introduction into interstate commerce  
1719 a modified risk tobacco product. Section 911(a) of the FD&C Act. FDA plans to issue  
1720 regulations pursuant to section 910(g) of the FD&C Act (21 U.S.C. 387j(g)) providing  
1721 conditions under which modified risk tobacco products may be exempted from the  
1722 requirements of section 911 of the FD&C Act when used for investigational purposes.  
1723 Until these regulations are issued, FDA will consider exercising discretion in enforcing  
1724 the requirements of section 911 of the FD&C Act, in some circumstances, for the  
1725 purposes of allowing investigational use of proposed modified risk tobacco products.

1726

1727 Specifically, at this time, FDA does not intend to enforce the requirements of section 911  
1728 of the FD&C Act with respect to the use of proposed modified risk tobacco products in  
1729 studies that follow the specifications listed below that will help ensure that the studies are

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1730 well-controlled, data derived from such studies are reliable, and study subjects are  
1731 adequately protected.

1732

1733 For all studies (both human and nonclinical), you should:

1734

- 1735 • Limit direct distribution of the proposed modified risk tobacco product to
- 1736 qualified and appropriately trained investigators;
- 1737 • Not promote for commercial distribution or test market the proposed modified
- 1738 risk tobacco product;
- 1739 • Account for receipt, use, and disposition of all investigational product(s), and
- 1740 • Label the product “for investigational use only.”

1741

1742 For human studies, you should:

1743

- 1744 • Take measures to ensure the reliability and validity of the study, for example,
- 1745 through sound study design and adherence to study protocol. In addition, you
- 1746 should ensure that all studies are conducted such that the rights, safety, and
- 1747 welfare of human subjects have been protected in accordance with ethical
- 1748 principles acceptable to the world community and that the data are scientifically
- 1749 valid. One approach to implementing such measures would be to conduct the
- 1750 study in accordance with appropriate provisions found in 21 CFR Part 50
- 1751 (informed consent of human subjects) and ensure that the IRB oversight is
- 1752 governed by 21 CFR Part 56 (IRB review and approval of clinical investigations).
- 1753 Additional information about informed consent and IRBs can be found in FDA’s
- 1754 guidance documents. Applicants with specific questions about human subject
- 1755 protections are encouraged to contact the Center for Tobacco Products.
- 1756 • Ensure that all study subjects receiving product be current daily tobacco product
- 1757 users at least 21 years of age.

1758

1759 For nonclinical studies, you should:

1760

- 1761 • Take measures to ensure the reliability and validity of the study. One approach to
- 1762 implementing such measures would be to follow good laboratory practices as
- 1763 specified in 21 CFR Part 58. Additional information about good laboratory
- 1764 practice regulations can be found in FDA’s guidance documents. Applicants with
- 1765 specific questions about good laboratory practice regulations are encouraged to
- 1766 contact the Center for Tobacco Products.

1767

1768 Applicants who would like to conduct research using their modified risk tobacco products  
1769 should contact the Office of Science at the Center for Tobacco Products to discuss the  
1770 submission of a study protocol and/or study endpoints for investigations intended to  
1771 support an MRTPA.

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1772 **B. Requesting a Meeting with FDA**

1773

1774 You should send your request for a meeting in writing to the Director of CTP’s Office of  
1775 Science at the following address:

1776

1777 Food and Drug Administration

1778 Center for Tobacco Products

1779 Document Control Center

1780 Building 71, Room G335

1781 10903 New Hampshire Avenue

1782 Silver Spring, MD 20993-0002

1783

1784 The meeting request should include adequate information for FDA to assess the potential  
1785 utility of the meeting and to identify FDA staff necessary to discuss the proposed agenda  
1786 items, including the following:

1787

1788 • A brief statement of the purpose of the meeting, including the name of your new  
1789 tobacco product, a brief description of the product, and the role of your planned  
1790 study(s) in overall product development plans;

1791 • A list of your specific questions grouped by discipline;

1792 • A proposed agenda, including objectives and outcomes expected from the  
1793 meeting;

1794 • A list of all individuals (including titles) expected to attend the meeting on your  
1795 behalf; and

1796 • An investigational plan to support the demonstrations required for issuance of an  
1797 order under section 911(g) of the FD&C Act.

1798

1799 We recommend that the summary of your proposed study protocol(s) include the  
1800 following information:

1801

1802 • Study objective(s);

1803 • Study hypotheses;

1804 • Background information (a brief description of the modified risk tobacco product  
1805 and any regulatory history);

1806 • Study design;

1807 • Study population (number of subjects to be enrolled, inclusion/exclusion criteria,  
1808 comparison group(s));

1809 • Human subject protection information, including IRB information;

1810 • Primary and secondary endpoints (definition and success criteria);

1811 • Statistical analysis plan (description of the statistical methods to be employed, the  
1812 reason for your choice of sample size, including calculations of the power of each  
1813 study and the level of significance and/or confidence level to be used);

1814 • Data collection procedures; and

• Baseline and follow-up assessments and duration of follow-up.



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1815 Pre-meeting preparation is critical for achieving a productive discussion or exchange of  
1816 information. After FDA schedules a meeting, we request that you submit a fully  
1817 paginated meeting package, organized according to the final agenda, containing a  
1818 detailed description of your product, the status of product development, an investigational  
1819 plan for evaluating whether the product meets the criteria for issuance of an order under  
1820 section 911(g) of the FD&C Act (including a summary of your proposed study  
1821 protocols), the specific questions to be discussed, and background information relevant to  
1822 those questions.

1823  
1824 FDA’s receipt of a complete meeting package, including clearly articulated questions for  
1825 FDA, well in advance of a meeting will enable FDA staff to review the information  
1826 adequately and is therefore important to achieving a productive meeting.

1827 **C. Studies Conducted Outside of the United States**

1828  
1829 You may submit studies of your product conducted outside the United States as part of  
1830 your MRTPA. You should follow the general principles for scientific studies and  
1831 analyses described in section VI.C. All human studies conducted outside the United  
1832 States should be conducted to ensure that the rights, safety, and welfare of human  
1833 subjects have been protected in accordance with ethical principles acceptable to the world  
1834 community and that the data are scientifically valid and applicable to the U.S. population.  
1835 The investigator should conduct these studies in conformance with international  
1836 standards for good clinical practices or obey the laws and regulations of the country in  
1837 which the research is conducted, whichever affords the greater protection of human  
1838 subjects. These patient protection and data integrity measures ensure that data from  
1839 studies conducted outside the United States are from adequate and well-designed studies  
1840 and provide reliable information to FDA.

1841 **X. Confidentiality**

1842  
1843 Information submitted under section 911 of the FD&C Act may include, but is not  
1844 limited to, a company’s non-public, trade secret, or confidential commercial information.  
1845

1846 Several laws govern the confidentiality of tobacco product information submitted under  
1847 section 911 of the FD&C Act, including sections 301(j) and 906(c) of the FD&C Act (21  
1848 U.S.C. 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. 1905), and the Freedom of  
1849 Information Act (FOIA) (5 U.S.C. 552) as well as FDA’s implementing regulations.

1850  
1851 FDA’s general regulations concerning the public availability of FDA records are  
1852 contained in 21 CFR Part 20.

1853  
1854 Section 911(e) of the FD&C Act requires FDA to make an MRTPA publicly available  
1855 except matters in the application, which are trade secrets or otherwise confidential,  
1856 commercial information. In order to facilitate FDA’s publication of the disclosable

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1857 portions of your MRTPA under section 911(e) for public comment, FDA recommends  
1858 that you identify the portions of the application you believe constitute trade secret or  
1859 confidential commercial information that is exempt from disclosure by either:

1860

- 1861 • Including in your cover letter a description or listing of such information; or
- 1862 • Submitting two versions of your application – a complete, unredacted version  
1863 and a second version with transparent highlights of the information you believe is  
1864 exempt from disclosure.

1865

1866 FDA will make the final evaluation regarding what information can be made publicly  
1867 available under section 911(e) of the FD&C Act.