

Guidance for Industry

Modified Risk Tobacco Product Applications

DRAFT GUIDANCE

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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 Industry¹

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance provides information about submitting applications for modified risk tobacco products under section 911 of the Federal Food, Drug, and Cosmetic Act (the FD&C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

¹ 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.

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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;² 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

250

251

252

253

² 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.³

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).

³ 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.”⁴ 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*

⁴ 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:⁵
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

⁵ 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 product⁶ (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

⁶ 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.⁷ Components, ingredients, and

⁷ 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, supported⁸, or possessed⁹, by the

⁸ 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.).

⁹ 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 manufacturer¹⁰ 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

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

685 FDA also recommends that applicants seeking risk modification orders submit:
686

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

690 FDA also recommends that applicants seeking exposure modification orders submit:
691

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

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 • The health risks associated with use of the product as compared to using other
710 tobacco products on the market, including tobacco products within the same class
711 of products;
712 • The changes in health risks to users who switch from using another tobacco
713 product to using the product, including tobacco products within the same class of
714 products;
715 • The health risks associated with switching to the product as compared to quitting
716 the use of tobacco products;
717 • The health risks associated with using the product in conjunction with other
718 tobacco products;
719 • The health risks associated with switching to the product as compared to using an
720 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;¹¹ 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;

¹¹ 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 nature¹² 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.¹³ Applicants should test for and report
906 on the HPHC list as established by FDA under section 904(d) of the FD&C Act.¹⁴

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.¹⁵ 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.

¹² 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.

¹³ 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>).

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

¹⁵ The ISO method is available at 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 evaluated¹⁶);
- 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;¹⁷ 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>);

¹⁶ 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.

¹⁷ 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.¹⁸

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

¹⁸ 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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- 1204 • Passive surveillance, which relies on spontaneous reports submitted by tobacco
1205 product manufacturers, health care professionals, or consumers; and
1206 • Active surveillance, which relies on an active collection of data. Data may be
1207 collected by local agencies (e.g., city, state, American Indian tribal) or through
1208 registries established by tobacco product manufacturers, published literature or
1209 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 • Data on real world use of the MRTP in a general population of tobacco users;
1216 • Tobacco-related adverse events;
1217 • Longer-term assessment of exposure and health outcomes, including intermediate
1218 clinical outcomes and mortality; and
1219 • Ongoing assessment of consumer perception and tobacco use behavior (e.g.,
1220 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*¹⁹

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.²⁰ 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

¹⁹ 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.

²⁰ 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
- 1362
- 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.²¹

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

²¹ 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
- 1454 size, and comparator groups;
- 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

1460

- The original study protocol(s) used;
- 1461 • Any amendments (which should be dated) to the study protocol;
- 1462 • The final study protocol;
- 1463 • A justification for the method selected, i.e. appropriateness for the evaluation
- 1464 of the selected endpoint;
- 1465 • All raw data and data files used to generate the results;
- 1466 • The questionnaires used;
- 1467 • Any transcripts or recordings of interviews and focus groups, where
- 1468 applicable;
- 1469 • Case report forms;
- 1470 • For nonclinical studies, documentation describing the actions taken to ensure
- 1471 reliability and validity of the study (for example, documentation of good
- 1472 laboratory practices as specified in 21 CFR Part 58);
- 1473 • Documentation describing the actions taken to ensure the protection of human
- 1474 subjects (for example, documentation of study oversight by a qualified
- 1475 Institutional Review Board duly constituted and operating under 21 CFR Part
- 1476 56, and documentation of informed consent procedures such as those
- 1477 described in 21 CFR Part 50);
- 1478 • A detailed description of the statistical analyses employed, including all
- 1479 variables, confounders, and subgroup analyses, and a full report of the
- 1480 findings;
- 1481 • Information on Data Monitoring Committee members;
- 1482 • Information on any contract research organization if obligations were
- 1483 transferred for the conduct of any study; and
- 1484 • Investigator expertise and credentials.

1485

1486 For each study, the report should also identify whether the study was conducted by or on

1487 the applicant's behalf.

1488

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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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- 1619
- 1620
- 1621
- 1622
- 1623
- 1624
- 1625
- 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 **D. What Happens After You Submit an MRTPA?**

1631

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,²² 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 **E. Can I Withdraw My Pending MRTPA?**

1650

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.

²² 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.²³

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,²⁴ 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.

²³ 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>).

²⁴ 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.