

Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health**

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Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. Introduction

This guidance presents the current thinking of FDA on principles for premarket review of combination products, including how to determine which type of premarket submission is appropriate.¹ This guidance offers general, high-level information relevant to combination products. The Agency has published guidance on premarket review issues relevant to specific categories of combination products² and will continue to use such guidance as needed to provide more detailed information on specific premarket considerations and specific types of combination products.

Section 3038 of the 21st Century Cures Act, enacted in December 2016 (P.L. 114-255) (“Cures Act”), substantially amended section 503(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 353(g)), the principal section of the FD&C Act expressly addressing

¹ Agency policy regarding postmarket regulation of combination products is outside the scope of this guidance. Agency regulations at 21 CFR Part 4, for example, codify the regulatory requirements for current good manufacturing practice requirements and for postmarketing safety reporting for combination products.

² See the Combination Products Guidance Documents web page at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm122047.htm>. Guidances mentioned in this document may also be available on the Biologics guidance web page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, and/or the Devices guidance web page at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm> and/or the Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

27 combination products. General themes of these amendments include enhancing clarity,
28 predictability, efficiency, and consistency of premarket regulatory expectations for combination
29 products, including by ensuring that Agency components and staff coordinate appropriately on
30 premarket review of these products, and that Agency thinking is aligned in conducting these
31 reviews.³ FDA is publishing this guidance as part of its efforts to implement Cures Act section
32 3038 and in keeping with the Agency’s long-standing commitment to transparency, efficiency,
33 and regulatory consistency, to facilitate development of safe and effective combination products.
34

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

41

42 **II. Combination product status and interaction with FDA**

43

44 **A. What are combination products and how are their Center assignments determined?**

45

46 As set forth in section 503(g) of the FD&C Act and 21 CFR part 3, a combination product is a
47 product composed of two or more different types of medical products (i.e., a combination of a
48 drug, device, and/or biological product with one another). The drugs, devices, and biological
49 products included in combination products are referred to as “constituent parts” of the
50 combination product.
51

52

53 Under 21 CFR 3.2(e), combination products include:

54

- 55 • A product comprised of two or more regulated components, i.e., drug/device,
56 biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or
57 otherwise combined or mixed and produced as a single entity (a “single entity”
58 combination product, such as a prefilled syringe or drug-eluting stent);
- 59 • Two or more separate products packaged together in a single package or as a unit and
60 comprised of drug and device products, device and biological products, or biological and
61 drug products (a “co-packaged” combination product, such as a surgical or first-aid kit
62 containing bandages and an antiseptic drug);
- 63 • A drug, device, or biological product packaged separately that according to its
64 investigational plan or proposed labeling is intended for use only with an approved,
65 individually specified drug, device, or biological product where both are required to
66 achieve the intended use, indication, or effect and where upon approval of the proposed
67

³ While not the focus of this guidance, section 3038 also amended section 503(g) to clarify premarket data and information expectations for combination products that include certain approved constituent parts. See 21 USC 353(g)(3).

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68 product the labeling of the approved product would need to be changed (e.g., to reflect a
69 change in intended use, dosage form, strength, route of administration, or significant
70 change in dose) (a “cross-labeled” combination product, as might be the case for a light-
71 emitting device and a light-activated drug indicated for use together for treatment of a
72 dermatologic condition); or

- 73
- 74 • Any investigational drug, device, or biological product packaged separately that
75 according to its proposed labeling is for use only with another individually specified
76 investigational drug, device, or biological product where both are required to achieve the
77 intended use, indication, or effect (also a “cross-labeled” combination product).
- 78

79 A combination product is assigned to an Agency Center that will have primary jurisdiction (i.e.,
80 “the lead”) for that combination product’s premarket review and regulation. Under section
81 503(g)(1), assignment of a combination product to a lead Center is based on a determination of
82 which constituent part provides the primary mode of action (PMOA) of the combination
83 product.⁴ If the PMOA of a device-biological product combination product is attributable to the
84 biological product, for example, the Center responsible for premarket review of such a biological
85 product would have primary jurisdiction for the regulation of the combination product. As
86 discussed in section II.B., the Agency Center with primary jurisdiction works with other Agency
87 Centers to ensure adequate premarket review.

88

89 You may submit a request for designation (RFD) if you wish to obtain a binding classification or
90 assignment determination from FDA, or a “Pre-RFD” to obtain informal feedback relating to the
91 classification or assignment of your product, including regarding preparation of an RFD.⁵

92

93 **B. Basics of interacting with FDA**

94

95 The lead Center is a sponsor’s primary point of contact and typically the Agency’s focal point for
96 presenting FDA’s views to the sponsor. The premarket processes and procedures of the lead
97 Center are available to and should be utilized by sponsors, including pre-submission meetings
98 and other mechanisms for obtaining Agency feedback.⁶

99

100 As provided in section 503(g)(8)(C)(iv), as added by the Cures Act, the Agency will ensure that
101 meetings between the FDA and sponsors are attended by review staff from each Center as
102 appropriate in light of the topics and purpose of the meeting, and that consulting Centers

⁴ The PMOA of a combination product is the single mode of action (drug, device, or biological product) expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. See section 503(g)(1)(C) (added by the Cures Act); see also 21 CFR 3.2(k) (which defines “mode of action” and “therapeutic”) and (m) (which presents a definition for primary mode of action that was codified by the Cures Act in section 503(g)).

⁵ See the guidance for industry *How to Write a Request for Designation (RFD)* (April 2011) and *How to Prepare a Pre-Request for Designation (Pre-RFD)* (February 2018).

⁶ As reflected in section 503(g)(7), the Agency will utilize appropriate Agency resources to ensure adequate review of safety, effectiveness, or substantial equivalence.

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103 complete their premarket reviews in a timely manner. As provided in section 503(g)(8)(C)(iii),
104 Agency communications regarding the review from the lead Center are considered
105 communications on behalf of all Centers involved with the review, to the extent consistent with
106 the provisions of law and requirements of all affected Centers. Accordingly, Centers are
107 expected to coordinate as appropriate prior to issuance of such communications.⁷
108

109 As provided in section 503(g)(8)(C)(v), sponsors may request in writing the participation of
110 representatives of the Office of Combination Products (OCP) in meetings regarding their
111 products, or to have OCP otherwise engage on regulatory matters concerning the product.
112 Sponsors, for example, may contact OCP for assistance, as needed, in identifying appropriate
113 contact points (including those in the lead Center), resolving substantive issues, or otherwise
114 facilitating interactions with the Agency and collaboration among Agency components. Center
115 dispute resolution mechanisms are available with respect to the substance of such reviews.
116

117 Please note that, under section 503(g)(8)(C)(v), sponsors are required to identify their products
118 as combination products in seeking Agency action with respect to the product.
119
120

121 **III. Basics of premarket regulation of combination products**
122

123 Drugs, devices, and biological products retain their discrete regulatory identities when they are
124 constituent parts of a combination product. Combination products also comprise a distinct
125 category of medical products that can be subject to specialized regulatory requirements.⁸ The
126 regulatory requirements for combination products arise from the statutory and regulatory
127 requirements applicable to drugs, devices, and biological products, which do not lose their
128 distinct regulatory identity when they become part of a combination product.⁹ Therefore, the
129 premarket requirements for demonstrating the safety and effectiveness of a combination product
130 as a whole derive from the statutory and regulatory requirements applicable to its constituent
131 parts.
132

⁷ See Staff Manual Guide 4101, *Inter-Center Consult Request Process* (June 2018) (<https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/staffmanualguides/ucm283569.pdf>), which describes expectations and processes for inter-Center consults between the Center for Devices and Radiologic Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER). See also Staff Manual Guide 4103, *Expectations and Procedures for Engagement among Medical Product Centers and Office of Combination Products on Regulations and Guidance Pertaining to Combination Products* (March 2018)

(<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM602810.pdf>), for a description of the expectations and procedures for engagement of the three Centers and the Office of Combination Products (OCP) for the development and clearance of regulations and guidance documents that pertain to combination products.

⁸ See combination product current good manufacturing practice and postmarketing safety reporting rules, 78 FR 4307-22 (2013) (21 CFR Part 4, Subpart A) and 81 FR 92603-26 (2016) (21 CFR Part 4, Subpart B).

⁹ *Ibid.*

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133 With regard to premarket authorization pathways, FDA’s current thinking is that a single
134 application¹⁰ is generally appropriate for a combination product.¹¹ The marketing application
135 type submitted should generally coincide with the PMOA of the combination product (e.g., a
136 PMA, De Novo, or 510(k) for a device-led combination product, an NDA or ANDA for a drug-
137 led combination product, or a BLA for a biologic-led combination product). FDA believes a
138 single application will streamline submission to and communication with the Agency and will
139 eliminate unnecessary duplication that may occur with multiple applications. To appropriately
140 assess the safety and effectiveness of a combination product in a single application, such
141 application should enable a substantially similar evaluation to that which would be applied to
142 each constituent part if they were reviewed under separate applications, including consideration
143 of data and information that would be reviewed under separate applications. If one type of
144 application coinciding with the PMOA of the combination product (PMOA-based application
145 type) does not enable such an evaluation, the combination product should typically be reviewed
146 in a different PMOA-based application type.¹² In limited cases, an application type associated
147 with the statutory authorities applicable to the non-lead constituent part (the constituent part
148 applicable to the non-lead Center) may be needed.¹³ If a sponsor believes a particular
149 application type is appropriate for other reasons, it should discuss with FDA. The Agency
150 anticipates that a single application may not be appropriate in limited cases.¹⁴

¹⁰ For purposes of this guidance, unless otherwise stated, the term “application” includes a new drug application (NDA), abbreviated new drug application (ANDA), premarket approval application (PMA), premarket notification (510(k) notification), request for classification submitted under section 513(f)(2) of the FD&C Act (De Novo request), or biologics license application (BLA), including a BLA submitted under section 351(k) of the PHS Act.

¹¹ See section 503(g)(1)(B) and 503(g)(6) of the FD&C Act (providing that “the Secretary shall conduct the premarket review of any combination product under a single application, whenever appropriate”) and that a sponsor may choose to submit separate applications for the different constituent parts of a combination product unless the FDA determines that a single application is necessary. However, the focus of this guidance is review of combination products for which marketing authorization is sought under a single application, though separate applications would generally be permissible for the constituent parts of cross-labeled combination products.

¹² For example, if an independent showing of safety and effectiveness would be needed for any constituent part then 510(k) would likely not be appropriate. Please refer to the Annex of this document and page 7 of the guidance for industry and Food and Drug Administration staff *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]* (July 2014).

¹³ See, for example, the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (Biosimilars Q&A Guidance) (December 2018), which discusses regulatory clarity and consistency considerations for why a BLA would be the more appropriate application type for antibody-drug conjugates, a type of drug-biologic combination product that is assigned to CDER regardless of the PMOA of the combination product. In this case, due to factors that included “[t]he relative significance of the safety and effectiveness questions raised by the constituent parts, particularly the highly specific molecular targeting by the antibody to a cell type, cellular component, or other marker at the site of action (as distinguished from mere alteration of systemic pharmacokinetics),” the Agency determined that a BLA was a more appropriate pathway to evaluate this type of combination product. In certain scenarios, similar considerations might arise when determining the appropriate application type for other combination products. In other cases, incorporation of a biologic component that is already licensed under section 351 of the PHS Act into the combination product is likely to be the most effective way to facilitate a substantially similar evaluation of a non-lead biologic constituent part in a drug or device application type.

¹⁴ Decisions with respect to which application type is appropriate and whether a single or separate applications are appropriate will generally require consultation and alignment between the lead and non-lead Center. See Staff Manual Guide 4101, *Inter-Center Consult Request Process* (June 2018)

(<https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/staffmanualguides/ucm283569.pdf>).

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151 In determining what is needed to demonstrate the safety and effectiveness of the combination
152 product as a whole, FDA takes into account the questions and considerations reflected in the
153 statutes and regulations for each constituent part. For example, for a device-led combination
154 product that includes a drug constituent part reviewed in an appropriate device application,
155 nonclinical pharmacology and toxicology and clinical pharmacology (including
156 pharmacokinetic) data and chemistry, manufacturing, and controls (CMC) information are
157 among the types of information that would typically be necessary. Similarly, for a device or
158 drug-led combination product that includes a biological constituent part reviewed in an
159 appropriate drug or device application, certain information, including regarding the identity of
160 the biological constituent part, and indicating compliance with donor eligibility or lot release
161 requirements, where applicable, would typically be necessary. Likewise, for a drug or biologic-
162 led combination product that includes a device constituent part reviewed in an appropriate drug
163 or biologic application, engineering, biocompatibility, performance data and other design
164 validation data would typically be necessary. Regardless of which Center may have the lead and
165 which application type may be appropriate, consistent with section 503(g) of the FD&C Act,
166 FDA is committed to applying a consistent, risk-based approach to address similar regulatory
167 questions, including scientific questions, similarly, utilizing relevant expertise from the lead and
168 consulted Centers.

169
170 It bears noting that the data and information needed to address safety and effectiveness questions
171 related to the non-lead constituent part of a combination product may differ from the data and
172 information needed to obtain marketing authorization for that article as a stand-alone product
173 that is not part of a combination product. For example, a drug may be coated on a device to
174 mitigate undesired local physiological responses associated with the implantation procedures or
175 the use of the product. Examples of this may include an anti-inflammatory drug on a cardiac
176 lead to reduce inflammation at the implantation site or an anti-coagulant bound to the inner-
177 lumen of a catheter to prevent clot formation within the catheter thereby maintaining catheter
178 patency. Given their role in supporting the function of the device, these drug coatings often
179 involve a lower dose and/or primarily local, rather than systemic, exposure to a drug as
180 compared to what it is otherwise approved for as a stand-alone drug product. As such, there may
181 be differing conditions of use for the drug due to the intended use in the context of the
182 combination product that may raise different safety and effectiveness concerns.

183
184 The premarket review of a combination product can be significantly streamlined in instances
185 where its sponsor is legally authorized to rely on FDA’s prior findings of safety or effectiveness
186 or substantial equivalence with respect to an approved or cleared constituent part, or where the
187 sponsor has a right of reference for another sponsor’s data. For an approved drug constituent
188 part, reliance on FDA’s prior findings of safety or effectiveness is permissible in a device
189 application, when scientifically appropriate, subject to the provisions of section 503(g)(5) of the
190 FD&C Act, as added by the Cures Act. A similar approach applies for drug-led combination
191 products where the sponsor has a right of reference to the data upon which a device was cleared
192 or approved. In such circumstances, FDA generally should only require additional data and
193 information as may be needed to address additional questions of safety or effectiveness raised by
194 the proposed use or function of the device in the combination product.

195

196 **IV. Pathway availability and related considerations**
197

198 This section discusses pathways available for combination products based on their PMOA, and
199 considerations for making such pathway determinations.
200

201 **A. Device-led combination products**
202

203 As discussed above, Cures Act section 3038 addressed various aspects of the regulation of
204 combination products. Among other matters, the legislation reflects the general availability of
205 the De Novo classification, PMA, and 510(k) pathways for device-led combination products.¹⁵
206 This discussion is intended to clarify Agency thinking on the availability of PMA, De Novo, and
207 510(k) pathways for device-led combination products, in light of Cures Act section 3038.
208

209 **1. Premarket Approval (PMA) Applications**
210

211 PMA approval is required by FDA before nearly all devices that are class III¹⁶ can be legally
212 marketed.¹⁷ PMA approval is based on a determination by FDA that the PMA contains
213 sufficient valid scientific evidence to assure that the device or device-led combination product is
214 safe and effective for its intended use(s).¹⁸ Sponsors should ensure that PMA applications for
215 device-led combination products contain sufficient data to demonstrate the safety and
216 effectiveness of the combination product as a whole, including data regarding all constituent
217 part(s). The PMA includes sections containing, among other things, technical data, non-clinical
218 laboratory studies, and clinical investigations.¹⁹ Before approving or denying a PMA, the

¹⁵ While beyond the scope of this guidance, section 3038 also included amendments to section 503(g) of the FD&C Act to subject device-led combination products to certain exclusivity and patent-related provisions applicable to new drug applications pursuant to section 505(b)(2) of the FD&C Act. See section 503(g)(5). For more information regarding these requirements please see the guidance for industry and Food and Drug Administration staff *Refuse to Accept Policy for 510(k)s* (January 2018) and *Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)* (January 2018).

¹⁶ Class III devices are devices (1) for which there is insufficient information to determine that general controls and special controls are sufficient to provide reasonable assurance of safety and effectiveness, and (2) which are purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or which present a potential unreasonable risk of illness or injury (see section 513(a)(1)(C) of the FD&C Act).

¹⁷ See section 515 of the FD&C Act.

¹⁸ For FDA to approve a PMA, there must be a reasonable assurance of safety and effectiveness. See section 515(d)(2)(A) and (B) of the FD&C Act. Effectiveness is determined on the basis of well-controlled investigations, including one or more clinical investigations, where appropriate, unless FDA determines there exists other valid scientific evidence sufficient to determine effectiveness, from which it can fairly and responsibly be concluded by qualified experts that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. Section 513(a)(3) of the FD&C Act.

¹⁹ See 21 CFR 814.20.

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219 appropriate FDA advisory committee²⁰ may review the PMA at a public meeting and provide
220 FDA with the committee’s recommendation on whether FDA should approve the submission.²¹

221
222 **2. De Novo Classification Requests**

223
224 Devices of a new type that FDA has not previously classified or reclassified based on the criteria
225 in section 513(a)(1) of the FD&C Act are automatically classified into class III by operation of
226 section 513(f)(1) of the FD&C Act, and may be classified into class I or class II under the De
227 Novo classification process. This section and the Annex discuss the availability of the De Novo
228 pathway for premarket review of device-led combination products.

229
230 If a sponsor believes its product is appropriate for classification into class I²² or class II,²³ it may
231 submit a De Novo request for classification.²⁴ If the sponsor demonstrates that the criteria in
232 section 513(a)(1)(A) or (B) of the FD&C Act are met, FDA grants the De Novo request for
233 classification and issues a written order classifying the specific product and product type in class
234 I or class II. If the product is classified as class II, it is granted marketing authorization subject
235 to general controls, as well as identified special controls which provide a reasonable assurance of
236 safety and effectiveness.²⁵ Such a product may serve as a legally marketed (predicate)²⁶ product
237 for future 510(k) submissions. If the product cannot be classified as class I or II, the De Novo
238 request is declined and the product remains in class III, subject to PMA approval.

239
240 Special controls set forth criteria for class II products that are necessary to provide the assurance
241 of safety and effectiveness to justify classification in class II. To be class II by being within the
242 same type as the product that was the subject of the De Novo, future products must be found
243 substantially equivalent and comply with applicable special controls for the product type; a

²⁰ For more information please see the guidance for industry and Food and Drug Administration staff *Procedures for Meetings of the Medical Devices Advisory Committee* (September 2017).

²¹ See 21 CFR 814.44.

²² Class I products are subject to a comprehensive set of regulatory authorities called general controls (see section 513(a)(1)(A) of the FD&C Act). General controls include, but are not limited to, provisions that relate to establishment registration and listing, premarket notification, prohibitions against adulteration and misbranding, records and reports, and good manufacturing practices.

²³ Class II products are products for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the product, and for which there is sufficient information to establish special controls necessary to provide such assurance (see section 513(a)(1)(B) of the FD&C Act). Special controls are product type-specific and may include promulgation of performance standards, requirements for postmarket surveillance, patient registries, labeling, and performance testing and clinical/non-clinical data.

²⁴ See section 513(f)(2) of the FD&C Act. See also the guidance for industry and Food and Drug Administration staff *De Novo Classification Process (Evaluation of Automatic Class III Designation)* (October 2017).

²⁵ Such special controls should be established through consultation and alignment with the non-lead Center.

²⁶ A legally marketed (predicate) device to which a new device may be compared for a determination regarding substantial equivalence is a device that was legally marketed prior to May 28, 1976, or a device which has been reclassified from class III to class II or I, or a device which has been found to be substantially equivalent through the 510(k) premarket notification process (see 21 CFR 807.92(a)(3)).

244 failure to comply with special controls will cause the product to be class III and subject to PMA
245 approval.²⁷

246
247 If a sponsor opts to directly submit a De Novo request without submitting a 510(k) first, FDA
248 may decline to undertake such request if FDA identifies a predicate product that could provide a
249 reasonable basis for review of substantial equivalence, or when FDA determines that the product
250 submitted is not of low to moderate risk or that general controls would be inadequate to control
251 the risks and special controls to mitigate the risks cannot be developed.²⁸ For example,
252 understanding of the biologic or drug constituent parts, including limitations of such
253 understanding, need to be considered when determining the suitability of the De Novo pathway
254 for such device-led combination products. Because certain products present unique concerns
255 (such as, for certain biologics,²⁹ considerations associated with infectious disease transmission
256 and challenges associated with ensuring reproducibility of such biologics), management of such
257 concerns should be considered in determining the suitability of the De Novo pathway.

258
259 See Annex for illustrative examples on how these principles can be applied.

260

3. Premarket Notification (510(k)) Submissions

261

262
263 The 510(k) review standard (substantial equivalence of a new product to a predicate product)
264 differs from the PMA and De Novo review standards. The 510(k) review standard is
265 comparative, whereas the PMA and De Novo review standards rely on an independent
266 demonstration of safety and effectiveness. Nonetheless, the principles of safety and
267 effectiveness underlie the substantial equivalence determination in every 510(k) review.

268

269 The standard for a determination of substantial equivalence in a 510(k) review is set out in
270 section 513(i) of the FD&C Act. A product is substantially equivalent to a predicate product if
271 it:

272

- 273 • has the same intended use as the predicate product; and
- 274
- 275 • has the same technological characteristics as the predicate product;
- 276

276

277 *or*

278

- 279 • has the same intended use as the predicate product;
- 280
- 281 • has different technological characteristics³⁰; and

²⁷ See sections 513(a)(1)(B), 513(f)(1), 513(i), and 515(a)(2) of the FD&C Act; S. REP. NO. 105-43 at 35 (1997).

²⁸ See section 513(f)(2)(A)(ii) and (iv) of the FD&C Act.

²⁹ For example, blood, gene therapies, or human cellular or tissue products.

³⁰ “Different technological characteristics” are defined as “significant change in the materials, design, energy source, or other features” from the predicate. Section 513(i)(1)(B) of the FD&C Act and 21 CFR 807.100(b)(2)(ii)(A).

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- 282 • the information submitted to FDA, including appropriate clinical or scientific data if
283 deemed necessary, demonstrates that the product:
284
285 ○ does not raise different questions of safety and effectiveness than the predicate
286 product; *and*
287
288 ○ demonstrates that the product is as safe and effective as a predicate product.³¹
289

290 FDA considers the product’s relative safety and effectiveness in the substantial equivalence
291 determination, and safety and effectiveness considerations are also critical to the Agency’s
292 evaluation of compliance with any applicable special controls, which FDA has determined to be
293 necessary to provide a reasonable assurance of safety and effectiveness for the product type.
294

295 The following products cannot be cleared in a 510(k) submission:
296

- 297 • Product with a new intended use as compared to the predicate product
298
299 • Product with different technological characteristics than the predicate product if such
300 differences raise different questions of safety and effectiveness than the predicate
301 product.³²
302

303 Generally, a device that is not combined with a drug or biologic constituent could not be
304 successfully used as a predicate for a 510(k) for a device-led combination product. This is
305 because the addition of the drug or biologic constituent would likely result in a new intended use
306 and/or constitute a different technological characteristic that raises different questions of safety
307 and effectiveness as compared to the predicate.
308

309 See Annex for illustrative examples on how these principles can be applied.
310

311 **B. Drug-led combination products**
312

313 An NDA or ANDA is generally the appropriate marketing authorization pathway for a drug-led
314 combination product. This discussion outlines current Agency thinking on the availability of the
315 NDA and ANDA pathways to obtain marketing authorization for drug-led combination products.
316

317 **1. New Drug Application (NDA)**
318

319 An NDA is generally the appropriate pathway for drug-led combination products other than
320 generic versions of already-approved drug-led combination products, which are discussed in the
321 next section. An NDA for a drug-led combination product must contain, among other things, a

³¹ See section 513(i)(1)(A) of the FD&C Act; 21 CFR 807.100(b). See also the guidance for industry and Food and Drug Administration staff *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]* (July 2014).

³² *Ibid.*

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322 demonstration of the safety and effectiveness of the product for the conditions prescribed,
323 recommended, or suggested in the proposed labeling.

324
325 There are two types of NDAs described in section 505 of the FD&C Act. A 505(b)(1)
326 application, also known as a “stand-alone” NDA, contains full reports of investigations of safety
327 and effectiveness that were conducted by or for the applicant or for which the applicant has a
328 right of reference or use. A 505(b)(2) application also contains full reports of investigations of
329 safety and effectiveness, but at least some of the safety or effectiveness information required for
330 approval comes from studies not conducted by or for the applicant and for which the applicant
331 has not obtained a right of reference or use.³³ Section 505(b)(2) permits reliance on FDA’s
332 finding of safety and effectiveness of an approved drug product (or an approved drug-led
333 combination product), as well as on published literature. The section 505(b)(2) pathway should
334 not be used to obtain approval of duplicates of existing drug-led combination products that are
335 eligible for approval under section 505(j) of the FD&C Act (see next section) (see 21 CFR
336 314.101(d)(9)). Both 505(b)(1) and 505(b)(2) applications are submitted under section 505(b)(1)
337 and approved under section 505(c) of the FD&C Act.

338
339 By way of example, a 505(b)(1) application may be appropriate for a drug-led combination
340 product that contains a new molecular entity, such as an inhaler copackaged with a novel
341 corticosteroid for treatment of asthma. A 505(b)(2) application may be appropriate, however, if
342 the corticosteroid has already been approved as an oral tablet and the sponsor seeks to rely upon
343 FDA’s finding of safety and effectiveness for the tablet dosage form in seeking approval of a
344 combination product composed of the corticosteroid formulated for inhalation and an inhaler,
345 provided that the 505(b)(2) applicant establishes a scientific bridge to demonstrate that reliance
346 on the oral tablet product is appropriate, any differences between the proposed and relied upon
347 products are supported, and the applicant complies with additional requirements, including but
348 not limited to requirements related to patent certification described in section 505(b)(2)&(3) of
349 the FD&C Act. In addition, approval of the 505(b)(2) application might be delayed because of
350 exclusivity or patent protections for a listed drug. A 505(b)(2) applicant could also rely, in part,
351 upon FDA’s NDA approval of an inhaler/corticosteroid combination product indicated for
352 treatment of asthma as one source of support for approval of a combination product consisting of
353 the same corticosteroid combined with an inhaler for treatment of chronic obstructive pulmonary
354 disease. Again the 505(b)(2) applicant would need to establish a scientific bridge to demonstrate
355 that reliance is appropriate, would need to submit data to support differences between the
356 products, would need to comply with requirements for a 505(b)(2) application (including but not
357 limited to requirements related to patent certification), and could be subject to delays in approval
358 due to the exclusivity or patent protections of a listed drug.

359
360
361
362

³³ See the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent FDA’s current thinking on this topic.

2. Abbreviated New Drug Application (ANDA)

363
364

365 An ANDA is generally the appropriate pathway for a drug-led combination product that has the
366 same active ingredient(s), dosage form, strength, route of administration, conditions of use, and
367 (with certain permissible differences) labeling as a product (i.e., a reference listed drug³⁴ (RLD))
368 previously approved under section 505(c) of the FD&C Act.³⁵ To obtain approval, an ANDA
369 applicant is not required to provide independent evidence to establish the safety and
370 effectiveness of the proposed product, as is required for an NDA. Instead, an ANDA relies on
371 FDA’s previous finding that the RLD is safe and effective.

372

373 In addition to the above, an ANDA must also include sufficient information to demonstrate that
374 the proposed product is bioequivalent³⁶ to the RLD, and to ensure the product’s identity,
375 strength, quality, and purity.

376

377 ANDAs for a drug-led combination product should also include sufficient information to
378 demonstrate that the non-lead constituent part is compatible for use with the final formulation of
379 the drug constituent part. For example, potential applicants should refer to relevant FDA
380 guidance documents and other sources that provide information on what data and information
381 should be included to support the delivery device constituent part(s) of a proposed generic
382 combination product.³⁷

383

384 As a general matter, in assessing the therapeutic equivalence of a proposed generic drug-device
385 combination, FDA will consider whether the proposed generic product can be substituted with
386 the expectation that it will have the same clinical effect and safety profile as the RLD when
387 administered to patients under the conditions specified in the labeling.³⁸ While, FDA does not
388 expect that the proposed generic combination product and its RLD be identical in all respects,
389 any differences identified between a proposed generic combination product and its RLD should
390 be adequately analyzed, scientifically justified, and otherwise not preclude approval under an
391 ANDA. The extent to which differences between the proposed generic combination product and
392 the RLD affect the approvability of the ANDA product will be evaluated on a case-by-case basis.

³⁴ A *reference listed drug* or RLD is “the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA” (21 CFR 314.3(b)). RLDs are identified in FDA’s list of *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the *Orange Book*, available at <https://www.accessdata.fda.gov/scripts/cder/ob/>. For purposes of this guidance the term RLD is also used to refer to such previously approved drug-led combination products.

³⁵ See generally sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 21 CFR 314.127.

³⁶ Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See 21 CFR 314.3(b).

³⁷ See the draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017). When final, this guidance will represent FDA’s current thinking on this topic.

³⁸ See 21 CFR 314.3. See also FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*), preface to the 38th edition, at page vii.

393 **C. Biologic-led combination products**
394

395 Most biological products are licensed through one of the two BLA pathways under section 351
396 of the Public Health Service Act (PHS Act), either under a section 351(a) BLA (i.e., a “stand-
397 alone” BLA) or under a section 351(k) BLA for a “biosimilar” or “interchangeable” biological
398 product.³⁹

399
400 **1. Biologics License Applications (BLAs) Submitted under Section 351(a)**
401

402 To be licensed, a biological product must be shown to be safe, pure, and potent and the facility in
403 which the biological product is manufactured, processed, packed, or held must meet standards
404 designed to ensure that the biological product continues to be safe, pure, and potent.⁴⁰ A BLA
405 submitted under section 351(a) of the PHS Act is a stand-alone application in that all of the
406 information and data necessary to demonstrate that these requirements are met are included in
407 the application. This pathway is generally appropriate for biologic-led combination products
408 other than products that are proposed to be biosimilar to, or interchangeable with, a previously
409 licensed biological product.⁴¹

410
411 For example, this pathway would be appropriate for the following products when the sponsor is
412 not seeking to rely on FDA’s licensure of another biological product in order to demonstrate
413 biosimilarity to, or interchangeability with, such product:

- 414 • a gene therapy combined with a specialized delivery catheter
 - 416 • a vaccine in a pre-filled syringe
 - 417 • a recombinant protein in an autoinjector
- 418
419
420

³⁹ Some protein products historically have been approved under section 505 of the FD&C Act. On March 23, 2010, the Biologics Price Competition and Innovation Act (BPCI Act) was enacted as part of the Patient Protection and Affordable Care Act (Public Law 111-148). The BPCI Act clarified the statutory authority under which certain protein products will be regulated by amending the definition of “biological product” in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized polypeptide),” and describing procedures for submission of a marketing application for certain biological products. The BPCI Act requires that a marketing application for a “biological product” (that previously could have been submitted under section 505 of the FD&C Act) must be submitted under section 351 of the PHS Act starting March 23, 2010. This requirement is subject to certain exceptions during a 10-year transition period ending on March 23, 2020. On March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act will be deemed to be a license for the biological product (i.e., an approved BLA) under section 351 of the PHS Act. After March 23, 2020, all sponsors seeking approval of a biological product that previously could have been submitted under section 505 of the FD&C Act will need to submit a marketing application under section 351 of the PHS Act. See the guidance for industry *Interpretation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009* (December 2018).

⁴⁰ Section 351(a)(2)(C) of the PHS Act.

⁴¹ See footnote 13.

421 **2. BLAs for Biosimilar and Interchangeable Biological Products Submitted**
422 **under Section 351(k)**
423

424 An abbreviated licensure pathway is available under section 351(k) of the PHS Act for products
425 shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference
426 product.⁴² Section 351(i)(2) of the PHS Act defines biosimilarity to mean that the product “is
427 highly similar to the reference product notwithstanding minor differences in clinically inactive
428 components” and that “there are no clinically meaningful differences” between the two products
429 with respect to safety, purity, and potency. To meet the interchangeability standard, an applicant
430 must show that its product “is biosimilar to the reference product,” and must further show that
431 the product “can be expected to produce the same clinical result as the reference product in any
432 given patient” and that, for a product that is administered more than once to an individual, “the
433 risk in terms of safety or diminished efficacy of alternating or switching between use of the [two
434 products] is not greater than the risk of using the reference product without such alternation or
435 switch.”⁴³ Interchangeable products may be substituted for the reference product without the
436 intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

437
438 FDA has published guidance indicating the availability of this abbreviated pathway for
439 combination products, as well as considerations related to demonstrating biosimilarity or
440 interchangeability of such products. With respect to demonstrating biosimilarity, Q. I.4 of the
441 guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act*
442 (Biosimilars Q&A Guidance) states that some design differences in the delivery device used with
443 the proposed biosimilar product may be permissible, and explains that it may be possible to
444 obtain licensure of a proposed biosimilar product in a pre-filled syringe or auto-injector, for
445 example, even though the reference product is a biological product licensed in a vial
446 presentation.

447
448 The Biosimilars Q&A Guidance also explains that licensure under section 351(k) would not be
449 possible if design difference in a delivery device results in any of the following:

- 450
- 451 • A clinically meaningful difference between the proposed product and the reference
452 product in terms of safety, purity, and potency;
 - 453
 - 454 • A different route of administration or dosage form; or
 - 455
 - 456 • A condition of use (e.g., indication, dosing regimen) for which the reference product has
457 not been previously approved;
 - 458

459 or otherwise does not meet the standard for biosimilarity.
460

⁴² Section 351(i)(4) of the PHS Act defines reference product to mean “the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)”.

⁴³ Section 351(k)(4) of the PHS Act.

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461 See Biosimilars Q&A Guidance for considerations for seeking licensure of a combination
462 product as biosimilar to, or interchangeable with, a reference product.⁴⁴

463

⁴⁴ See also the draft guidance for industry *Considerations in Demonstrating Interchangeability with a Reference Product* (January 2017). When final, this guidance will represent FDA's current thinking on this topic.

ANNEX

**Analysis of Pathway Availability for Device-Led Combination Products –
Illustrative Examples**

To date, questions regarding pathway availability for combination products have focused most often on device-led combination products. Accordingly, we have included this Annex to address common questions utilizing the analyses discussed in section IV.A. The outcomes are also consistent with the expectations discussed in section III, that the application enable evaluation substantially similar to that which would occur if the constituent parts were reviewed under separate applications for the use.

These hypothetical examples are not intended to reflect a complete analysis of the premarket review considerations that need to be addressed for the types of products discussed in the examples or other types of combination products. In addition, specific products may raise distinct issues that are not taken into account in the examples below. If manufacturers have specific questions relating to their particular products, the Agency recommends that they contact the lead Center for the product or OCP, as needed, for assistance.

For the purposes of the below illustrative examples, it is assumed that the sponsor submitted a 510(k) to CDRH for the combination product.

Example 1: *Antimicrobial coating added for the first time to a previously classified device type*

Predicate Product: A previously classified hypothetical class II device, with no drug or biologic constituent part, which is subject to 510(k) requirements (e.g., an externally-communicating device intended to be implanted in the abdominal cavity for drainage of excessive fluids).

Drug Constituent Part: A hypothetical antimicrobial coating (Antimicrobial A) that contains the same active ingredient that is in an NDA drug product approved for intravenous administration that has a well-established and understood risk profile as an antimicrobial indicated for the treatment of acute bacterial skin and skin structure infections. The sponsor has provided FDA documentation of a right of reference to the NDA.⁴⁵

New Product: The sponsor proposes to add an antimicrobial coating (Antimicrobial A) to the predicate product described above, making a single-entity combination product (hereinafter referred to as “Product A”). The purpose of adding the antimicrobial to this device is to prevent infections associated with the surgical procedure and continued use of the product. The sponsor requests the product be considered substantially equivalent to the previously cleared uncoated version of the device. An antimicrobial drug product has never been combined with this device type. To make a substantial equivalence determination, the following questions are generally asked:

⁴⁵ Alternatively, pursuant to section 503(g)(5), the sponsor could rely on FDA’s previous findings of safety and effectiveness for the NDA for Antimicrobial A, provided all of the requirements of 503(g)(5)(A) & (C) are satisfied.

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- 506 1. *Is the predicate product legally marketed? Yes.*
507
508 2. *Does the predicate product have the same intended use?* While both the predicate and
509 the new combination product are intended to drain excessive fluid from the abdominal
510 cavity, the addition of the proposed drug constituent part and the indication of preventing
511 infection was not applicable to the predicate product. These changes raise different
512 questions of safety and effectiveness, precluding a meaningful comparison with the
513 predicate product.⁴⁶ Therefore, these changes in indications for use of the product and its
514 constituent part would result in a new intended use and the product would be found not
515 substantially equivalent (NSE). Also, the addition of Antimicrobial A is a different
516 technological characteristic that would raise different questions of safety and
517 effectiveness.

518
519 Further, in this case the 510(k) pathway would not allow for an evaluation substantially similar
520 to that which would be applied to the drug constituent part under a separate application (see
521 section III). Specifically, comparison of the new product to the predicate would not allow for a
522 sufficient demonstration of the safety and effectiveness of the drug constituent part for its
523 proposed new conditions of use – both the new drug indication and the combined use of the drug
524 with the device.

525
526 Depending on its ability to meet the criteria in section 513(a)(1)(A) or (B) and 513(f)(2) of the
527 FD&C Act, the product may be a suitable candidate for the De Novo process. In determining
528 whether to grant a request for De Novo classification, because the sponsor in this example has a
529 right of reference to the data in the drug sponsor’s NDA, FDA would consider this data in its
530 review of the De Novo request. See discussion in Section III. If the product does not meet the
531 requirements for De Novo classification, a PMA would be required.

532
533 For purposes of this illustrative example, it is assumed that the sponsor demonstrates that the
534 criteria in section 513(a)(1)(B) (class II) of the FD&C Act are met. Accordingly, FDA has
535 determined that the safety and effectiveness of Product A can be reasonably assured by a
536 combination of general and special controls and Product A is granted marketing authorization.

537
538 Further, in this case, the De Novo pathway, including the NDA data incorporated in the
539 submission via the right of reference, permits an evaluation substantially similar to that which
540 would be applied to the drug constituent part under a separate application (see section III).
541 Specifically, a demonstration that general and special controls provide a reasonable assurance of
542 safety and effectiveness is sufficient to demonstrate the safety and effectiveness of the change to
543 the drug constituent part.

544
545 The classification regulation regarding Product A identifies the drug constituent part as being
546 limited to “Antimicrobial A.” Table 1 below shows an illustrative example of identified risks

⁴⁶ See 21 CFR 807.92(a)(5) and the guidance for industry and Food and Drug Administration staff *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]* (July 2014).

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547 and potential mitigation measures and special controls for each risk for a product such as Product
548 A.

549

550 **Table 1 – Identified Risks and Potential Mitigations for Product A**

551

Identified Risks	Potential Mitigation Measures	Potential Special Controls
Toxicity	<ul style="list-style-type: none"> ▪ Biocompatibility evaluation ▪ Animal performance testing/study information ▪ Clinical data ▪ Labeling ▪ Post-market surveillance (e.g., evaluate potential drug-related toxicity in a broader population) 	<ul style="list-style-type: none"> ▪ Clinical data must demonstrate lack of unreasonable risk of illness or injury associated with the use of the product under anticipated conditions of use. ▪ In vivo (animal) evaluation⁴⁷ must demonstrate lack of unreasonable risk of illness or injury associated with the use of the product under anticipated conditions of use. ▪ Labeling must include: <ul style="list-style-type: none"> - Information on the patient population for which the device has been demonstrated to be effective with the combination product. - A detailed summary of the non-clinical and/or clinical testing pertinent to use of the combination product. - A detailed summary of the device- and procedure-related adverse events pertinent to use of the combination product. ▪ Post-market surveillance (PMS) must be conducted and completed in accordance with FDA-agreed-upon PMS protocol.
Inability to prevent infection	<ul style="list-style-type: none"> ▪ Clinical data on effectiveness ▪ Animal study information ▪ Non-clinical bench performance testing (e.g., assays) ▪ Labeling 	<ul style="list-style-type: none"> ▪ Clinical data must demonstrate ability to prevent infection as intended for its anticipated conditions of use. ▪ In vivo (animal) evaluation must demonstrate ability to prevent infection as intended for its anticipated conditions of use. ▪ Assays must demonstrate antibacterial activity of the product. ▪ Same labeling special controls as outlined above.
Product failure/malfunction	<ul style="list-style-type: none"> ▪ Technical specifications/Technological characteristics ▪ Chemistry ▪ Stability 	<ul style="list-style-type: none"> ▪ The technical specifications of the combination product must include [specific parameters for a particular product], to ensure the combination product retains appropriate performance characteristics. ▪ Drug constituent part and drug-device finished combination product characterization must be included. ▪ Validated protocols must be provided and demonstrate ability to establish technical specifications. ▪ Performance data must support the stability of the product by demonstrating continued functionality over the identified shelf life.

552

553

554

⁴⁷ We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider whether such an alternative method could be assessed for equivalency to an animal test method.

555 **Example 2:** *New drug indication added*

556

557 **Predicate Product:** Product A described above.

558

559 **Drug Constituent Part:** The same drug constituent part as Product A. The sponsor has
560 provided FDA documentation of a right of reference to the NDA.

561

562 **New Product:** The sponsor subsequently proposes a new anti-inflammatory indication for
563 Product A, due to the pharmacological properties of the drug constituent part. The intent is not
564 only to maintain the previously supported use regarding the product’s antimicrobial properties,
565 but to also demonstrate an increase in its overall performance by reducing inflammation in the
566 host environment following implantation.

567

568 1. *Is the predicate product legally marketed?* Yes.

569

570 2. *Does the predicate product have the same intended use?* No. While both products are
571 intended to drain excessive interstitial fluid from the abdominal cavity, the new anti-
572 inflammatory indication and the associated labeling regarding reducing inflammation were
573 not applicable to the predicate product. These changes raise different questions of safety
574 and effectiveness, precluding a meaningful comparison with the predicate product.
575 Therefore, these changes in indications for use of the product and its constituent part would
576 result in a new intended use and the product would be found NSE.

577

578 Further, in this case the 510(k) pathway would not allow for an evaluation substantially similar
579 to that which would be applied to the drug constituent part under a separate application (see
580 section III). Specifically, comparison of the new product to the predicate (Product A) would not
581 allow for a sufficient demonstration of the safety and effectiveness of the drug constituent part
582 for the proposed new drug indication.

583

584

585 **Example 3:** *Different method of drug coating*

586

587 **Predicate Product:** Product A described above.

588

589 **Drug Constituent Part:** The same drug constituent part as Product A. The sponsor has
590 provided FDA documentation of a right of reference to the NDA.

591

592 **New Product:** The sponsor proposes to modify Product A by altering the method of drug
593 coating by using a polyurethane-drug coating solution as compared to the drug coating alone that
594 was used in Product A. The intent of the change is to mitigate drug release from the device
595 constituent part, thereby preventing potential adverse reactions and toxicities, while maintaining
596 effectiveness of the drug.

597

598 1. *Is the predicate product legally marketed?* Yes.

599

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- 600 2. *Does the predicate product have the same intended use?* Yes. There is no change to the
601 intended use or labeling.
602
- 603 3. *Do the products have the same technological characteristics?* No. The products do not
604 have the same technological characteristics as there are significant changes in the
605 materials and other features of this product from those of the predicate product. The
606 proposed product has a different coating and therefore a different formulation of the drug
607 as compared to Product A.
608
- 609 4. *Do the different technological characteristics of the product raise different questions of*
610 *safety and effectiveness that were not otherwise considered with the predicate product?*
611 No. The different technological characteristics of the products do not raise different
612 questions of safety and effectiveness since the safety and effectiveness questions
613 surrounding the different coating (e.g., with respect to drug release, safety and
614 effectiveness profile, infection rate, biocompatibility) were applicable to the predicate
615 product.
616
- 617 5. *Are methods available to evaluate the different technological characteristics' effects on*
618 *safety and effectiveness?* Yes. FDA reviews performance data (e.g., bench, animal,
619 and/or clinical) to determine whether such differences pose a significant safety or
620 effectiveness concern for the new product. This information is necessary to demonstrate
621 the new product is substantially equivalent to Product A and/or is compliant with the
622 applicable special controls.
623
- 624 6. *Do the data demonstrate substantial equivalence?* FDA would assess the submission,
625 including performance data to determine substantial equivalence, and would also assess
626 compliance with applicable special controls. If the performance data fail to demonstrate
627 substantial equivalence, or there is not compliance with the applicable special controls,
628 the product would be NSE.
629

630 We note that in this case, the 510(k) pathway permits an evaluation substantially similar to that
631 which would be applied to the drug constituent part under a separate application (see section III).
632 Specifically, a demonstration of substantial equivalence and compliance with the special controls
633 could be sufficient to demonstrate the safety and effectiveness of the change to the drug
634 constituent part. In this hypothetical, provided substantial equivalence and compliance with
635 applicable special controls are demonstrated, the proposed device-led combination product
636 would be granted marketing authorization.
637

638

639 **Example 4:** *Same drug constituent part with a lower concentration*

640

641 **Predicate Product:** Product A described above.

642

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643 **Drug Constituent Part:** The same drug constituent part as Product A. However, the drug
644 constituent part that is impregnated into the surface has a lower concentration (e.g., changed
645 from 500 µg/cm to 400 µg/cm). The sponsor has provided FDA documentation of a right of
646 reference to the NDA.

647
648 **New Product:** The only change the sponsor proposes to Product A is to include a lower
649 concentration of the drug constituent part that is impregnated into the surface by lowering it from
650 500 µg/cm to 400 µg/cm as compared to Product A. The intent is to maintain the product's
651 effectiveness but reduce the amount of the drug that might be released from the product, thereby
652 mitigating the potential for adverse reactions to the drug.

- 653
- 654 1. *Is the predicate product legally marketed?* Yes.
 - 655
 - 656 2. *Does the predicate product have the same intended use?* Yes. There is no change to the
657 intended use or labeling.
 - 658
 - 659 3. *Do the products have the same technological characteristics?* No. The products do not
660 have the same technological characteristics as there are significant changes in the
661 materials and other features of this product from those of the predicate product. The
662 proposed product has a lower concentration of the drug.
 - 663
 - 664 4. *Do the different technological characteristics of the product raise different questions of*
665 *safety and effectiveness that were not otherwise considered with the predicate product?*
666 No. The different technological characteristics of the products do not raise different
667 questions of safety and effectiveness since the safety and effectiveness questions
668 surrounding the concentration of the drug were applicable to the predicate product. For
669 example, these questions include ones related to release and safety and effectiveness
670 profile at the proposed drug concentration, as well as infection rate.
 - 671
 - 672 5. *Are methods available to evaluate the different technological characteristics' effects on*
673 *safety and effectiveness?* Yes, FDA reviews performance data (including clinical data
674 when necessary) to determine whether such differences pose a significant safety or
675 effectiveness concern for the new product. This information is necessary to demonstrate
676 the new product is substantially equivalent to Product A and/or is compliant with the
677 applicable special controls.
 - 678
 - 679 6. *Do the data demonstrate substantial equivalence?* FDA would assess the submission,
680 including performance data to determine substantial equivalence, and would also assess
681 compliance with applicable special controls. If the performance data fail to demonstrate
682 substantial equivalence, or there is not compliance with the applicable special controls,
683 the product would be NSE.
 - 684

685 We note that in this case, the 510(k) pathway permits an evaluation substantially similar to that
686 which would be applied to the drug constituent part under a separate application (see section III).
687 Specifically, a demonstration of substantial equivalence and compliance with the special controls

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688 could be sufficient to demonstrate the safety and effectiveness of the change to the drug
689 constituent part. In this hypothetical, provided substantial equivalence and compliance with
690 applicable special controls are demonstrated, the proposed device-led combination product
691 would be granted marketing authorization.
692

693

694 **Example 5:** *Replacing a drug constituent part with a different antimicrobial*

695

696 **Predicate Product:** Product A described above.

697

698 **Drug Constituent Part:** An NDA approved drug product containing a different antimicrobial
699 active ingredient that is indicated for the treatment of acute bacterial skin and skin structure
700 infections (Antimicrobial B). The sponsor has provided FDA documentation of a right of
701 reference to the NDA for Antimicrobial B.
702

703

704 **New Product:** The sponsor replaces Antimicrobial A in Product A with a different antimicrobial
705 that has also been approved in an NDA (Antimicrobial B). The sponsor does not change the
706 indications or directions for use of the new product as compared to Product A.

707

708 In this example, the special controls in the classification regulation regarding Product A resulting
709 from FDA granting the De Novo request specifically require the active ingredient in the drug
710 constituent part to be the active ingredient in Antimicrobial A.⁴⁸ As the new product contains a
711 different active ingredient from Product A, it would not be within the same type, and would thus
712 be NSE. Even if the special controls did not specify a particular active ingredient, a product with
713 a different active ingredient from a predicate would differ significantly in features such as design
714 and materials, which would likely raise different questions of safety and effectiveness and cause
715 the product to be NSE.

716

717 Further, in this case the 510(k) pathway would not allow for an evaluation substantially similar
718 to that which would be applied to the drug constituent part under a separate application (see
719 section III). Specifically, comparison of the new product to the predicate would not allow for a
720 sufficient demonstration of the safety and effectiveness of the drug constituent part for its
721 proposed new conditions of use for Antimicrobial B – both the new drug indication and the
combined use of the drug with the device.

⁴⁸ In certain instances, it may be possible for special controls to specify multiple specific active ingredients or an active ingredient class, provided general and special controls are sufficient to provide a reasonable assurance of safety and effectiveness for the product.