

Principles of Premarket Pathways for Combination Products

Guidance for Industry and FDA Staff

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

This guidance represents 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 office 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.¹ This guidance offers general, high-level information regarding what combination products are, coordination within FDA and interaction between FDA and sponsors regarding combination product regulation, and how combination products are reviewed by FDA before they are marketed. The remainder of this guidance focuses on how to determine which type of premarket submissions may be appropriate for 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 U.S.C. 353(g)), the principal section of the FD&C Act expressly addressing combination products. General themes of these amendments include enhancing clarity, predictability, efficiency, and consistency of premarket regulatory expectations for combination products, including by ensuring that Agency components and staff coordinate appropriately on premarket review of these products, and that Agency thinking is aligned in conducting these

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 practices and for postmarketing safety reporting for combination products.

² We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, which includes a link to the Combination Products Guidance Documents web page.

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reviews.³ FDA is publishing this guidance as part of its efforts to implement Cures Act section 3038 and in keeping with the Agency's long-standing commitment to transparency, efficiency, and regulatory consistency, to facilitate development of safe and effective combination products.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. COMBINATION PRODUCT STATUS AND INTERACTION WITH FDA

A. What Are Combination Products and How Are Their Center Assignments Determined?

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

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

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (a *single entity* combination product, such as a prefilled syringe or drug-eluting stent);
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (a *co-packaged* combination product, such as a surgical or first-aid kit containing bandages and an antiseptic drug);
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved, individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose) (a *cross-labeled* combination product, as might be the case for a light-

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 section 503(g)(3) of the FD&C Act.

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emitting device and a light-activated drug indicated for use together for treatment of a dermatologic condition); or

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

A combination product is assigned to an Agency center that will have primary jurisdiction (i.e., *the lead*) for that product's regulation. Under section 503(g)(1), assignment of a combination product to a lead center is based on a determination of which constituent part provides the primary mode of action (PMOA) of the combination product.⁴ If the PMOA of a device-biological product combination product is attributable to the biological product, for example, the center responsible for premarket review of such a biological product would have primary jurisdiction for the regulation of the combination product. As discussed in section II.B., the Agency center with primary jurisdiction works with other Agency centers to ensure appropriate, consistent regulation.

If you are uncertain or disagree with a center on product classification or which center is the lead for a particular product, you may submit a request for designation (RFD) to obtain a binding classification and/or assignment determination from FDA, or a Pre-RFD to obtain informal feedback relating to the classification and/or assignment of your product, including regarding preparation of an RFD. While sponsors may propose the classification and/or assignment they believe should apply for a pre-RFD, and must do so for an RFD, the Office of Combination Products (OCP) makes the final determination with input from the relevant Agency components.⁵ The referenced guidances describe the information FDA needs to conduct these assessments and the processes FDA uses for making these determinations.⁶

B. Basics of Interacting With FDA

The lead center is a sponsor's primary point of contact and typically the Agency's focal point for presenting FDA's views to the sponsor. The premarket processes and procedures of the lead center are available to and should be used by sponsors, including pre-submission meetings and

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) and 21 CFR 3.2(m); see also 21 CFR 3.2(k) (which defines *mode of action* and *therapeutic*).

⁵ If OCP does not respond to an RFD within 60 days of filing, the classification or assignment proposed by the sponsor will become the final determination. See section 563(d) of the FD&C Act and 21 CFR 3.8(b).

⁶ 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).

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other mechanisms for obtaining Agency feedback.⁷ While this general approach is available for and generally should be used for all combination products, cross-labeled combination products for which separate marketing authorizations are being sought for the constituent parts (e.g., a new drug application (NDA) for the drug and a premarket notification (510(k)) for the device) can raise distinct considerations. Prior to the filing of separate marketing authorization submissions, all interactions with FDA should be through the lead center for these combination products, regardless of the feedback being requested. The sponsor(s) may wish to discuss with the centers (and OCP as needed) how best to ensure efficient, coordinated engagement during review of marketing authorization submissions (e.g., in light of the differing user fee performance goals associated with the submission types for each constituent part).⁸

As provided in section 503(g)(8)(C)(iv), the centers, in conjunction with OCP when needed, will ensure that meetings between the FDA and sponsors are attended by review staff from each center as appropriate in light of the topics and purpose of the meeting, and that consulting centers complete their premarket reviews in a timely manner.⁹ As provided in section 503(g)(8)(C)(iii), Agency communications regarding the review from the lead center are considered communications on behalf of all centers involved with the review, to the extent consistent with the provisions of law and requirements of all affected centers. Accordingly, centers are expected to coordinate as appropriate prior to issuance of such communications.¹⁰

As provided in section 503(g)(8)(C)(v), sponsors may request in writing the participation of representatives of OCP in meetings regarding their products, or to have OCP otherwise engage on regulatory matters concerning the product. Sponsors, for example, may contact OCP for

⁷ As reflected in section 503(g)(7), the Agency will utilize appropriate Agency resources to ensure adequate review of safety, effectiveness, or substantial equivalence. For additional information regarding ways in which combination product sponsors can obtain feedback from FDA on scientific and regulatory questions and best practices for FDA and sponsors when interacting on these topics, see the guidance for industry and FDA staff *Requesting FDA Feedback on Combination Products* (December 2020).

⁸ As reflected in section II.A, sponsors that are uncertain of whether their products are constituent parts of a cross-labeled combination product may contact OCP.

⁹ While OCP does not routinely engage on product-specific review matters, as a general matter the office is required to: coordinate inter-center premarket reviews for combination products; oversee their timeliness and the alignment of feedback to the sponsor; ensure there is a primary point of contact(s) in the lead center; coordinate communications between lead and consulting centers if requested; ensure meetings with the sponsor are attended by each center as appropriate; ensure that the consulting center(s) advise as appropriate on relevant regulations, guidance, and policies; hear disputes concerning timeliness of premarket review; and consult on disputes regarding the substance of premarket review that have been presented to the Commissioner in accordance with the requirements of section 503(g)(8)(E)(ii). See section 503(g)(8) of the FD&C Act.

¹⁰ 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 Radiological 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 OCP for the development and clearance of regulations and guidance documents that pertain to combination products.

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assistance, as needed, in identifying appropriate contact points (including those in the lead center), resolving substantive issues, or otherwise facilitating interactions with the Agency and collaboration among Agency components. Center dispute resolution mechanisms are available with respect to the substance of such reviews.¹¹

Please note that, under section 503(g)(8)(C)(v), sponsors are required to identify their products as combination products in seeking Agency action with respect to the product. It is important that combination products be identified on the appropriate form or document: Form FDA 1571, INVESTIGATIONAL NEW DRUG APPLICATION; Form FDA 356h, APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE; or in the cover letter of a pre-investigational new drug application (IND) submission, investigational device exemption (IDE) application, Q-submission, 510(k) submission, premarket approval application (PMA), and/or request for classification submitted under section 513(f)(2) of the FD&C Act (De Novo request).¹²

III. BASICS OF PREMARKET REGULATION OF COMBINATION PRODUCTS

The regulatory requirements for combination products arise from the statutory and regulatory requirements applicable to drugs, devices, and biological products, which retain their discrete regulatory identities when they are constituent parts of a combination product.¹³ At the same time, combination products comprise a distinct category of medical products that can be subject to specialized regulatory requirements, where appropriate.¹⁴ Specialized regulatory requirements for combination products generally are designed to address the overlaps and distinctions between the statutory and regulatory requirements applicable to the drug, device, and biological product constituent parts that comprise them.

Section 503(g)(1)(B) and 503(g)(6) of the FD&C Act provide that FDA “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 FDA “determines that a single application is necessary.” FDA’s current thinking is that a single application¹⁵ would generally be appropriate for a combination product, to streamline regulatory interactions with the Agency and to avoid unnecessary

¹¹ See guidance for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (November 2017), guidance for industry and Food and Drug Administration staff *Center for Devices and Radiological Health (CDRH) Appeals Processes* (July 2019), and draft guidance for industry *Requests for Reconsideration at the Division Level Under GDUFA* (October 2017) (when final, this guidance will represent FDA’s current thinking on this topic).

¹² See guidance for industry and Food and Drug Administration staff *Refuse to Accept Policy for 510(k)s* (September 2019), *Acceptance Review for De Novo Classification Requests* (October 2021), and *Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)* (December 2019).

¹³ 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).

¹⁴ *Ibid.*

¹⁵ For purposes of this guidance, unless otherwise stated, the term *application* includes an NDA, abbreviated new drug application (ANDA), PMA, 510(k), De Novo request, or biologics license application (BLA), including a BLA submitted under section 351(k) of the PHS Act.

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duplication that may occur with multiple applications. However, separate applications would generally be permissible for the constituent parts of a cross-labeled combination product; when using such an approach applicants should coordinate with both centers (and may request OCP assistance), to help enable efficient, timely consideration of issues that may be relevant to each constituent part, or both, and to their combined use, including with respect to changes during the product lifecycle to either constituent part. In limited situations, FDA may determine that a single application is not appropriate and thus that an application for each constituent part is warranted.

The marketing application type submitted should generally coincide with the PMOA of the combination product (a PMA, De Novo, or 510(k) for a device-led combination product; an NDA or ANDA for a drug-led combination product; or a BLA for a biologic-led combination product). To appropriately ensure the safety and effectiveness of a combination product in a single application, such application should enable a substantially similar evaluation to that which would be applied to each constituent part if they were reviewed under separate applications (e.g., an ANDA or NDA for a drug and a PMA, De Novo, or 510(k) for a device), including consideration of data and information that would be reviewed under the separate applications. If one type of application coinciding with the PMOA of the combination product (PMOA-based application type), e.g., an ANDA, does not enable such an evaluation for each constituent part, the combination product should typically be reviewed in a different application type, e.g., an NDA, that still coincides with the PMOA of the combination product.¹⁶ In limited cases, FDA has determined that the product should be reviewed under an application type associated with the statutory authorities applicable to the non-lead constituent part.¹⁷ If a sponsor believes a particular application type is appropriate for other reasons, it should discuss with FDA.

Further, in determining what is needed to demonstrate the safety and effectiveness of the combination product, FDA takes into account the questions and considerations, reflected in the statutory and regulatory provisions associated with each constituent part in its review of the combination product as a whole and its constituent parts. This includes how the constituent parts

¹⁶ 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).

¹⁷ See, for example, the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (Biosimilars Q&A Guidance) (September 2021), 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 “the 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 PK [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 such as those containing certain biologics (e.g., blood products and products composed of or containing live cells or microorganisms). In other cases, incorporation of a biological product 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 biological product constituent part.

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may interact and interrelate. For example, for a device-led combination product reviewed in an appropriate device application that includes a drug constituent part (that would otherwise be reviewed in an NDA), nonclinical pharmacology and toxicology and clinical pharmacology (including pharmacokinetic) data and chemistry, manufacturing, and controls (CMC) information are among the types of information that would typically be necessary. Similarly, for a combination product that is not biologic-led and includes a biological product constituent part, certain information, including regarding the identity of the biological product constituent part, and indicating compliance with donor eligibility or lot release requirements, where applicable, would typically be necessary.¹⁸ Likewise, for a combination product that is not device-led and includes a device constituent part, engineering, biocompatibility, performance data, and other design validation data would typically be necessary. Regardless of which center may have the lead and which application type may be appropriate, consistent with section 503(g) of the FD&C Act, FDA is committed to applying a consistent, risk-based approach to address similar regulatory questions, including scientific questions, similarly, utilizing relevant expertise from the lead and consulted centers.¹⁹

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

¹⁸ As additional examples in the case of a drug or device-led combination product that includes a biological product constituent part, commercial scale process validation data, information sufficient to enable FDA to conduct pre-approval inspections of the proposed commercial product during manufacturing operations, and information demonstrating that the applicant has knowledge of and direct control over the manufacturing process for the biological product constituent part (rather than by reference to a drug or device master file) if the biological product constituent part is not licensed for that use, typically would be necessary to include in a marketing application to support a determination that the combination product is safe and effective. Please note that the examples provided in this guidance are not an exhaustive list. Failure to provide this information may result in FDA refusing to file the marketing application.

¹⁹ The Food and Drug Administration Modernization Act of 1997 and subsequent statutory amendments by the Food and Drug Administration Safety and Innovation Act and the Cures Act directed FDA to take a *least burdensome* approach to medical device premarket evaluation. The least burdensome concept and Agency guidance interpreting this concept, accordingly, also apply to device constituent parts of combination products. See the guidance for industry and Food and Drug Administration staff *The Least Burdensome Provisions: Concept and Principles* (February 2019). While the statutory least burdensome expectation does not apply to drugs or biological products, FDA is committed to the principle of avoiding unnecessary regulatory burden for all medical products including combination products.

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The premarket review of a combination product can be significantly streamlined in instances where its sponsor is legally authorized to rely on FDA’s finding of safety and/or effectiveness or substantial equivalence with respect to a previously approved or cleared combination product or constituent part, or where the sponsor has a right of reference for another sponsor’s data.²⁰ For a device-led, device-drug combination product containing an *approved drug* (as defined in section 503(g)(5)(B) of the FD&C Act²¹), reliance on FDA’s finding of safety and/or effectiveness for the approved drug is permissible in a device application, when scientifically appropriate, subject to the provisions of section 503(g)(5), as added by the Cures Act.²² A similar approach applies for drug-led combination products where the sponsor has a right of reference to the data upon which a device or device-led combination product was cleared or approved. In such circumstances, FDA generally should only require additional data and information as may be needed to address additional questions of safety or effectiveness raised by the proposed use or function of the device in the combination product, if any.²³

IV. PATHWAY AVAILABILITY AND RELATED CONSIDERATIONS

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

A. Device-Led Combination Products

As discussed above, Cures Act section 3038 addressed various aspects of the regulation of combination products. Among other matters, the legislation reflects and clarifies the availability

²⁰ Master files may be useful tools when several applications are submitted for different products which use a common material, process, etc., such as a platform delivery device, to help preserve the trade secrets of a third party such as a supplier or facility. Please note that the adequacy of relevant information contained in master files to support safety and effectiveness is considered only in the context of a specific marketing application referencing such files. For more information on biologics, device, and drug master files, see CBER’s [Master Files for CBER-Regulated Products](https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/master-files-cber-regulated-products) web page (available at <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/master-files-cber-regulated-products>), CDRH’s [Master Files](https://www.fda.gov/medical-devices/premarket-approval-pma/master-files) web page (available at <https://www.fda.gov/medical-devices/premarket-approval-pma/master-files>), and CDER’s [Drug Master Files](https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs) (DMF) web page (available at <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>), respectively, and FDA’s proposed rule on *Biologics License Applications and Master Files* (84 FR 30968, June 28, 2019).

²¹ In relevant part, the definition states that “‘approved drug’ means an active ingredient that was in an application previously approved under section 505(c)...relied upon by the applicant [for the combination product].”

²² See also section 520(h)(4) of the FD&C Act regarding permissibility of using information from an approved PMA.

²³ For additional information regarding data requirements when adding or changing a constituent part of a combination product and the bridging mechanisms that may be available to leverage relevant existing data, see the draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products* (December 2019). When final, this guidance will represent FDA’s current thinking on this topic.

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of the PMA, De Novo classification, and 510(k) pathways for device-led combination products.²⁴ This discussion and the annex are intended to clarify Agency thinking on the availability of PMA, De Novo, and 510(k) pathways for device-led combination products, in light of Cures Act section 3038.

1. Premarket Approval Applications (PMA)

PMA approval is required by FDA before devices that are class III²⁵ can be legally marketed.²⁶ PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to reasonably assure that the device or device-led combination product is safe and effective for its intended use(s).²⁷ Sponsors should ensure that PMA applications for device-led combination products contain sufficient data to demonstrate the safety and effectiveness of the combination product as a whole, including data regarding all constituent part(s). The PMA includes sections containing, among other things, technical data, non-clinical laboratory studies, and clinical investigations.²⁸ Before approving or denying a PMA, the appropriate FDA advisory committee²⁹ may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission.³⁰

2. De Novo Classification Requests

Devices of a new type that FDA has not previously classified or reclassified based on the criteria in section 513(a)(1) of the FD&C Act are automatically classified into class III by operation of section 513(f)(1) of the FD&C Act, and may be classified into class I or class II under the De Novo classification process.

²⁴ 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 see the guidance for industry and Food and Drug Administration staff *Refuse to Accept Policy for 510(k)s and Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)*.

²⁵ 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).

²⁶ See section 515 of the FD&C Act.

²⁷ 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.

²⁸ See 21 CFR 814.20.

²⁹ For more information see the guidance for industry and Food and Drug Administration staff *Procedures for Meetings of the Medical Devices Advisory Committee* (September 2017).

³⁰ See 21 CFR 814.44.

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If a sponsor believes its product is appropriate for classification into class I³¹ or class II,³² it may submit a request for De Novo classification.³³ If the sponsor demonstrates that the criteria in section 513(a)(1)(A) or (B) of the FD&C Act are met, FDA grants the request for De Novo classification and issues a written order classifying the specific product and product type in class I or class II. If the product is classified as class II, it is granted marketing authorization subject to general controls, as well as identified special controls which provide a reasonable assurance of safety and effectiveness.³⁴ Such a product may serve as a legally marketed (predicate)³⁵ product for future 510(k) submissions. If the product cannot be classified as class I or II, the De Novo request is declined and the product remains in class III and subject to PMA approval.

Special controls set forth criteria for class II products that are necessary to provide the assurance of safety and effectiveness to justify classification in class II. To be class II by being within the same type as the product that was the subject of the De Novo, future products must be found substantially equivalent and comply with general controls and applicable special controls for the product type; a failure to comply with special controls will cause the product to be class III and subject to PMA approval.³⁶

A sponsor may request De Novo classification without submitting a 510(k) first; FDA may decline to undertake such request if FDA identifies a predicate product that could provide a reasonable basis for review of substantial equivalence, or if FDA determines either that the product submitted is not of low to moderate risk or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.³⁷ Among other considerations, understanding of the biological product or drug constituent parts, including limitations of such understanding, need to be considered when determining the suitability of the De Novo pathway for such device-led combination products. Because certain products present unique concerns (such as, for certain biological products,³⁸ considerations associated with infectious disease transmission and challenges associated with ensuring reproducibility of such

³¹ Class I products are subject to a 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.

³² 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.

³³ See section 513(f)(2) of the FD&C Act and 21 CFR part 860, subpart D (86 FR 54826, October 5, 2021). See also the guidance for industry and Food and Drug Administration staff *De Novo Classification Process (Evaluation of Automatic Class III Designation)* (October 2021).

³⁴ Such special controls will generally be established through consultation and alignment with the non-lead center.

³⁵ 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)).

³⁶ 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).

³⁷ See section 513(f)(2)(A)(ii) and (iv) of the FD&C Act.

³⁸ For example, blood, gene therapies, or human cellular or tissue products.

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biological products), management of such concerns should be considered in determining the suitability of the De Novo pathway.

See annex for illustrative examples on how these principles can be applied.

3. Premarket Notification (510(k)) Submissions

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

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

- has the same intended use as the predicate product; and
- has the same technological characteristics as the predicate product;

or

- has the same intended use as the predicate product;
- has different technological characteristics³⁹; and
- the information submitted to FDA, including appropriate clinical or scientific data if deemed necessary, demonstrates that the product:
 - does not raise different questions of safety and effectiveness than the predicate product; *and*
 - demonstrates that the product is as safe and effective as the predicate product.⁴⁰

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

³⁹ *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).

⁴⁰ 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)]*.

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

- Product with a new intended use as compared to the predicate product
- Product with different technological characteristics than the predicate product if such differences raise different questions of safety and effectiveness than the predicate product.⁴¹

Generally, a device that is not combined with a drug or biological product constituent part could not be successfully used as a predicate for a 510(k) for a device-led combination product. This is because the addition of the drug or biological product constituent part would likely result in a new intended use and/or constitute a different technological characteristic that raises different questions of safety and effectiveness as compared to the predicate. In addition, a product with a different active ingredient from a predicate would differ significantly in features such as design and materials, which would likely raise different questions of safety and effectiveness as well.⁴²

See annex for illustrative examples on how these principles can be applied.

B. Drug-Led Combination Products

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

1. New Drug Application (NDA)

An NDA is generally the appropriate pathway for drug-led combination products other than generic versions of already-approved drug-led combination products. An NDA for a drug-led combination product must contain, among other things, a demonstration of the safety and effectiveness of the product for the conditions prescribed, recommended, or suggested in the proposed labeling.

There are two types of NDAs described in section 505 of the FD&C Act. A 505(b)(1) application, also known as a *stand-alone* NDA, contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use. A 505(b)(2) application also contains full reports of investigations of safety and effectiveness, but at least some of the safety or effectiveness information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.⁴³ Section 505(b)(2) permits reliance on FDA's

⁴¹ Ibid.

⁴² 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.

⁴³ 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.

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finding of safety and/or effectiveness for an approved drug product (or an approved drug-led combination product), as well as on published literature. The 505(b)(2) pathway should not be used to obtain approval of duplicates of existing drug-led combination products that are eligible for approval under section 505(j) of the FD&C Act (see next section) (see 21 CFR 314.101(d)(9)). Both 505(b)(1) and 505(b)(2) applications are submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act.

By way of example, a 505(b)(1) application may be appropriate for a drug-led combination product that contains a new molecular entity, such as a novel corticosteroid for treatment of asthma delivered via inhalation. The drug-device combination product may, for example, be an inhalation aerosol (also known as a metered dose inhaler (MDI) or inhalation powder (also known as a dry powder inhaler (DPI))). These products consist of a drug formulation and a container closure system that includes, or is, a device constituent part. A 505(b)(2) application may be appropriate, however, if, for example, the corticosteroid has already been approved as an oral tablet and the sponsor seeks to rely upon FDA's finding of safety and/or effectiveness for the tablet dosage form in seeking approval of a drug-device combination product (MDI or DPI consisting of the drug formulation containing the corticosteroid and the container closure system that includes, or is, the device constituent part), provided that the 505(b)(2) applicant establishes a scientific bridge to demonstrate that the extent of reliance on the oral tablet product is scientifically appropriate, any differences between the proposed and relied upon products are otherwise supported, and the applicant complies with additional requirements, including but not limited to requirements related to patent certification described in section 505(b)(2)&(3) of the FD&C Act.⁴⁴ A 505(b)(2) applicant could also rely, in part, upon FDA's NDA approval of a drug-device combination product containing the corticosteroid indicated for treatment of asthma as one source of support for approval of a drug-device combination product containing the same corticosteroid for treatment of chronic obstructive pulmonary disease. Again, the 505(b)(2) applicant would need to establish a scientific bridge to demonstrate that reliance is appropriate, would need to submit data to support differences between the products, and would need to comply with requirements for a 505(b)(2) application (including but not limited to requirements related to patent certification).⁴⁵

2. Abbreviated New Drug Application (ANDA)

An ANDA is generally the appropriate pathway for a drug-led combination product that has the same active ingredient(s), dosage form, strength, route of administration, conditions of use, and (with certain permissible differences) labeling as a product (i.e., a reference listed drug⁴⁶ (RLD)) previously approved under section 505(c) of the FD&C Act.⁴⁷ In addition to the above, an

⁴⁴ In addition, approval of the 505(b)(2) application might be delayed because of exclusivity or patent protections for a listed drug.

⁴⁵ Ibid.

⁴⁶ 21 CFR 314.3(b). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as the *Orange Book*, available at <https://www.accessdata.fda.gov/scripts/cder/ob/>.

⁴⁷ See generally sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 314.127.

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ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent⁴⁸ to the RLD, and to ensure the product's identity, strength, quality, and purity. To obtain approval, an ANDA applicant is not required to provide independent evidence to establish the safety and effectiveness of the proposed product; instead, an ANDA relies on FDA's finding that the RLD is safe and effective.

ANDAs for drug-led combination products should include sufficient information to demonstrate that the non-lead constituent part is compatible for use with the final formulation of the drug constituent part. Potential applicants should refer to relevant FDA guidance documents and other sources that provide information on what data and information should be included to support a device constituent part(s) of a proposed generic combination product (e.g., information analyzing the proposed user interface for a generic drug-device combination product when compared to the user interface for the RLD).⁴⁹

As a general matter, in assessing the therapeutic equivalence of a proposed generic drug-device combination product, FDA intends to consider whether the proposed generic product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling.⁵⁰ While FDA does not expect the proposed generic combination product and its RLD to be identical in all respects, any differences identified between a proposed generic combination product and its RLD should be adequately analyzed, scientifically justified, and otherwise not preclude approval under an ANDA. The extent to which differences between the proposed generic combination product and the RLD affect the approvability of the ANDA product will be evaluated on a case-by-case basis.

C. Biologic-Led Combination Products

Biologic-led combination products are licensed through one of the two BLA pathways under section 351 of the Public Health Service Act (PHS Act), either under a section 351(a) BLA (i.e.,

⁴⁸ 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).

⁴⁹ 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.

⁵⁰ See 21 CFR 314.3. See also the *Orange Book*, preface to the 41st edition, at page vii.

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a *stand-alone* BLA) or under a section 351(k) BLA for a *biosimilar* or *interchangeable* biological product.⁵¹

1. Biologics License Applications (BLAs) Submitted Under Section 351(a)

To be licensed, a biological product must be shown to be safe, pure, and potent, and the facility in which the biological product is manufactured, processed, packed, or held must meet standards designed to ensure that the biological product continues to be safe, pure, and potent.⁵² A BLA submitted under section 351(a) of the PHS Act is a stand-alone application in that all of the information and data necessary to demonstrate that these requirements are met are included in the application. This pathway is generally appropriate for biologic-led combination products other than products that are proposed to be biosimilar to, or interchangeable with, a previously licensed biological product.⁵³

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

- a gene therapy combined with a specialized delivery catheter
- a vaccine in a pre-filled syringe
- a protein product in an autoinjector

2. BLAs for Biosimilar and Interchangeable Biological Products Submitted Under Section 351(k)

⁵¹ 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 of 2009 (BPCI Act) was enacted as part of the Patient Protection and Affordable Care Act (Public Law 111-148). The BPCI Act amended the statutory definition of *biological product* in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)" and described procedures for submission of a marketing application for certain biological products. On December 20, 2019, the Further Consolidated Appropriations Act, 2020 (Public Law 116-94), further amended the statutory definition of *biological product* in section 351(i) of the PHS Act to remove the parenthetical "(except any chemically synthesized polypeptide)" from the statutory category of *protein*. On March 23, 2020, the Agency codified its interpretation of the statutory term *protein* in 21 CFR 600.3(h)(6) (85 FR 10057). The BPCI Act also required 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, subject to certain exceptions during a 10-year transition period ending on March 23, 2020. As of March 23, 2020, all approved applications for biological products under section 505 of the FD&C Act were deemed to be licenses for the biological products (i.e., approved BLAs) under section 351 of the PHS Act. As of 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 must submit a marketing application under section 351 of the PHS Act. For additional information, 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).

⁵² Section 351(a)(2)(C) of the PHS Act.

⁵³ See footnote 17.

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Section 351(k) of the PHS Act sets forth the requirements for the licensure of biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product.⁵⁴ Section 351(i)(2) of the PHS Act defines biosimilarity to mean that the product “is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences” between the two products with respect to safety, purity, and potency. To meet the interchangeability standard, an applicant must show that its product “is biosimilar to the reference product,” and must further show that the product “can be expected to produce the same clinical result as the reference product in any given patient” and that, for a product that is administered more than once to an individual, “the risk in terms of safety or diminished efficacy of alternating or switching between use of the [two products] is not greater than the risk of using the reference product without such alternation or switch.”⁵⁵ Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

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

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

- A clinically meaningful difference between the proposed product and the reference product in terms of safety, purity, and potency;
- A different route of administration;
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved; or
- A proposed biosimilar product that otherwise does not meet the standard for biosimilarity.

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

⁵⁴ Section 351(i)(4) of the PHS Act.

⁵⁵ Section 351(k)(4) of the PHS Act.

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 illustrative examples below, 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 (product has no drug or biological product 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.⁵⁶

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

⁵⁶ Alternatively, the sponsor could rely on FDA's finding of safety and/or effectiveness for the NDA approved antimicrobial product, provided all of the requirements of 503(g)(5)(A) and (C) are satisfied and it is scientifically justified. FDA may then consider such findings in its review of a device premarket submission.

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type. To make a substantial equivalence determination, the following questions are generally asked:

1. *Is the predicate product legally marketed?* Yes.
2. *Does the predicate product have the same intended use?* While both the predicate and the new combination product are intended to drain excessive fluid from the abdominal cavity, the addition of the proposed drug constituent part and the indication of preventing infection are not applicable to the predicate product. These changes raise different questions of safety and effectiveness, precluding a meaningful comparison with the predicate product.⁵⁷ Therefore, these changes in indications for use of the product and of adding the constituent part would result in a new intended use, and the product would be found not substantially equivalent (NSE). Also, the addition of Antimicrobial A is a different technological characteristic that would raise different questions of safety and effectiveness.

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

Depending on its ability to meet the criteria in section 513(a)(1)(A) or (B) and 513(f)(2) of the FD&C Act, the product may be a suitable candidate for the De Novo process. In determining whether to grant a request for De Novo classification, because the sponsor in this example has a right of reference to the data in the drug sponsor's NDA, FDA would consider this data in its review of the De Novo request.⁵⁸ See discussion in section III. If the product does not meet the requirements for De Novo classification, a PMA would be required.

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

Further, in this case, the De Novo pathway, including the NDA data incorporated in the submission via the right of reference, permits an evaluation substantially similar to that which would be applied to the drug constituent part under a separate application (see section III).⁵⁹ Specifically, a demonstration that general and special controls provide a reasonable assurance of

⁵⁷ 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)]*.

⁵⁸ If the applicant were able to rely upon findings of safety and effectiveness supporting the NDA approval, to the extent scientifically justified and subject to the requirements of section 503(g)(5), FDA could consider them in determining whether to grant the De Novo.

⁵⁹ *Ibid.*

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safety and effectiveness is sufficient to demonstrate the safety and effectiveness of the change to the drug.

The classification regulation regarding Product A identifies the drug constituent part as being limited to *Antimicrobial A*. Table 1 below shows an illustrative example of identified risks and potential mitigation measures and special controls for each risk for Product A and follow-on combination products seeking to use Product A as a predicate for the same intended use.

Table 1 – Identified Risks and Potential Mitigations for Product A

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) evaluation⁶⁰ 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 combination product has been demonstrated to be effective. - A detailed summary of the non-clinical and/or clinical testing pertinent to use of the combination product. - A detailed summary of the product- 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 for its anticipated conditions of use. ▪ In vivo (animal) evaluation must demonstrate ability to prevent infection 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.

⁶⁰ 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.

Example 2: *New drug indication added*

Predicate Product: Product A described above, which was granted a De Novo classification.

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

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

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

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

The proposed product would require an approved PMA before it could be legally marketed. Alternatively, the product may be suitable for a new De Novo classification.

Example 3: *Different method of drug coating*

Predicate Product: Product A described above, which was granted a De Novo classification.

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

New Product: The sponsor proposes to modify Product A by altering the method of drug coating by using a polyurethane-drug coating solution. A polyurethane coating was not used in Product A. The intent of the change is to mitigate drug release from the device constituent part, thereby preventing potential adverse reactions and toxicities, while maintaining effectiveness of the drug.

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1. *Is the predicate product legally marketed?* Yes.
2. *Does the predicate product have the same intended use?* Yes. There is no change to the intended use or labeling.
3. *Do the products have the same technological characteristics?* No. The products do not have the same technological characteristics as there are significant changes in the materials and other features of this product from those of the predicate product. The proposed product has a different coating and therefore a different formulation of the drug as compared to Product A.
4. *Do the different technological characteristics of the product raise different questions of safety and effectiveness that were not otherwise considered with the predicate product?* No. The different technological characteristics of the products do not raise different questions of safety and effectiveness since the safety and effectiveness questions surrounding the different coating (e.g., with respect to this drug's release, safety and effectiveness profile, infection rate, biocompatibility) were applicable to the predicate product.
5. *Are methods available to evaluate the different technological characteristics' effects on safety and effectiveness?* Yes. FDA reviews performance data (e.g., bench, animal, and/or clinical) to determine whether such differences pose a significant safety or effectiveness concern for the new product. This information is necessary to demonstrate the new product is substantially equivalent to Product A and/or is compliant with the applicable special controls.
6. *Do the data demonstrate substantial equivalence?* FDA would assess the submission, including performance data to determine substantial equivalence, and would also assess compliance with applicable special controls. If the performance data fail to demonstrate substantial equivalence, or there is not compliance with applicable special controls, the product would be NSE.

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

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

Predicate Product: Product A described above, which was granted a De Novo classification.

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

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

1. *Is the predicate product legally marketed?* Yes.
2. *Does the predicate product have the same intended use?* Yes. There is no change to the intended use or labeling.
3. *Do the products have the same technological characteristics?* No. The products do not have the same technological characteristics as there are significant changes in the materials and other features of this product from those of the predicate product. The proposed product has a lower concentration of the drug.
4. *Do the different technological characteristics of the product raise different questions of safety and effectiveness that were not otherwise considered with the predicate product?* No. The different technological characteristics of the products do not raise different questions of safety and effectiveness since the safety and effectiveness questions surrounding the concentration of this drug were applicable to the predicate product. For example, these questions include ones related to release and safety and effectiveness profile at the proposed drug concentration, as well as infection rate.
5. *Are methods available to evaluate the different technological characteristics' effects on safety and effectiveness?* Yes, FDA reviews performance data (including clinical data when necessary) to determine whether such differences pose a significant safety or effectiveness concern for the new product. This information is necessary to demonstrate the new product is substantially equivalent to Product A and/or is compliant with the applicable special controls.
6. *Do the data demonstrate substantial equivalence?* FDA would assess the submission, including performance data to determine substantial equivalence, and would also assess compliance with applicable special controls. Here, the special controls require clinical data to demonstrate the ability to prevent infection for its anticipated conditions of use, in this case the lower concentration of the drug. If the performance data fail to demonstrate

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substantial equivalence, or there is not compliance with applicable special controls, the product would be NSE.

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

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

Predicate Product: Product A described above, which was granted a De Novo classification.

Drug Constituent Part: A different hypothetical antimicrobial that contains an active ingredient that is in another NDA approved drug product indicated for the treatment of acute bacterial skin and skin structure infections (Antimicrobial B). The sponsor has provided FDA documentation of a right of reference to the NDA for this different antimicrobial.

New Product: The sponsor replaces Antimicrobial A in Product A with Antimicrobial B. The sponsor does not change the indications or directions for use of the new product as compared to Product A.

In this example, the special controls in the classification regulation regarding Product A resulting from FDA granting the De Novo request specifically require the active ingredient in the drug constituent part to be the active ingredient in Antimicrobial A. As the new product contains a different active ingredient from Product A, it would not be within the same type, and would thus be NSE. Even if the special controls did not specify a particular active ingredient, a product with a different active ingredient from a predicate would differ significantly in features such as design and materials, which would likely raise different questions of safety and effectiveness and cause the product to be NSE.⁶¹

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

The proposed product would require an approved PMA before it could be legally marketed. Alternatively the product may be suitable for a new De Novo classification.

⁶¹ See footnote 42.