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

DRAFT GUIDANCE

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 products[2] 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.

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 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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and 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 composed 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

[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).

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-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 combination product's premarket review and 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 adequate premarket review.

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

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 utilized by sponsors, including pre-submission meetings and other mechanisms for obtaining Agency feedback.[6]

As provided in section 503(g)(8)(C)(iv), as added by the Cures Act, the Agency 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

[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.

complete their premarket reviews in a timely manner. 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.[7]

As provided in section 503(g)(8)(C)(v), sponsors may request in writing the participation of representatives of the Office of Combination Products (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 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.

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.

III. Basics of premarket regulation of combination products

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

[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.

With regard to premarket authorization pathways, FDA's current thinking is that a single application[10] is generally appropriate for a combination product.[11] The marketing application type submitted should generally coincide with the PMOA of the combination product (e.g., 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). FDA believes a single application will streamline submission to and communication with the Agency and will eliminate unnecessary duplication that may occur with multiple applications. To appropriately assess 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, including consideration of data and information that would be reviewed under separate applications. If one type of application coinciding with the PMOA of the combination product (PMOA-based application type) does not enable such an evaluation, the combination product should typically be reviewed in a different PMOA-based application type.[12] In limited cases, an application type associated with the statutory authorities applicable to the non-lead constituent part (the constituent part applicable to the non-lead Center) may be needed.[13] If a sponsor believes a particular application type is appropriate for other reasons, it should discuss with FDA. The Agency anticipates that a single application may not be appropriate in limited cases.[14]

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[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).

In determining what is needed to demonstrate the safety and effectiveness of the combination product as a whole, FDA takes into account the questions and considerations reflected in the statutes and regulations for each constituent part. For example, for a device-led combination product that includes a drug constituent part reviewed in an appropriate device application, 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 device or drug-led combination product that includes a biological constituent part reviewed in an appropriate drug or device application, certain information, including regarding the identity of the biological constituent part, and indicating compliance with donor eligibility or lot release requirements, where applicable, would typically be necessary. Likewise, for a drug or biologic-led combination product that includes a device constituent part reviewed in an appropriate drug or biologic application, 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.

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 as 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.

The premarket review of a combination product can be significantly streamlined in instances where its sponsor is legally authorized to rely on FDA's prior findings of safety or effectiveness or substantial equivalence with respect to an approved or cleared constituent part, or where the sponsor has a right of reference for another sponsor's data. For an approved drug constituent part, reliance on FDA's prior findings of safety or effectiveness is permissible in a device application, when scientifically appropriate, subject to the provisions of section 503(g)(5) of the FD&C Act, as added by the Cures Act. A similar approach applies for drug-led combination products where the sponsor has a right of reference to the data upon which a device 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.

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 the general availability of the De Novo classification, PMA, and 510(k) pathways for device-led combination products.[15] This discussion is 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 (PMA) Applications

PMA approval is required by FDA before nearly all devices that are class III[16] can be legally marketed.[17] PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device or device-led combination product is safe and effective for its intended use(s).[18] 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.[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.

appropriate FDA advisory committee[20] may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission.[21]

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. This section and the Annex discuss the availability of the De Novo pathway for premarket review of device-led combination products.

If a sponsor believes its product is appropriate for classification into class I[22] or class II,[23] it may submit a De Novo request for classification.[24] 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 De Novo request for 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.[25] Such a product may serve as a legally marketed (predicate)[26] 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, 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 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)).

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

If a sponsor opts to directly submit a De Novo request 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 when FDA determines 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.[28] For example, understanding of the biologic 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 biologics,[29] considerations associated with infectious disease transmission and challenges associated with ensuring reproducibility of such biologics), 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 characteristics[30]; 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).

- 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 a predicate product.[31]

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, which FDA has determined to be necessary to provide a reasonable assurance of safety and effectiveness for the product type.

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.[32]

Generally, a device that is not combined with a drug or biologic constituent 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 biologic constituent 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.

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, which are discussed in the 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.

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.[33] Section 505(b)(2) permits reliance on FDA's finding of safety and effectiveness of an approved drug product (or an approved drug-led combination product), as well as on published literature. The section 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 an inhaler copackaged with a novel corticosteroid for treatment of asthma. A 505(b)(2) application may be appropriate, however, if the corticosteroid has already been approved as an oral tablet and the sponsor seeks to rely upon FDA's finding of safety and effectiveness for the tablet dosage form in seeking approval of a combination product composed of the corticosteroid formulated for inhalation and an inhaler, provided that the 505(b)(2) applicant establishes a scientific bridge to demonstrate that reliance on the oral tablet product is appropriate, any differences between the proposed and relied upon products are 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. In addition, approval of the 505(b)(2) application might be delayed because of exclusivity or patent protections for a listed drug. A 505(b)(2) applicant could also rely, in part, upon FDA's NDA approval of an inhaler/corticosteroid combination product indicated for treatment of asthma as one source of support for approval of a combination product consisting of the same corticosteroid combined with an inhaler 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, would need to comply with requirements for a 505(b)(2) application (including but not limited to requirements related to patent certification), and could be subject to delays in approval due to the exclusivity or patent protections of a listed drug.

[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)

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 drug[34] (RLD)) previously approved under section 505(c) of the FD&C Act.[35] To obtain approval, an ANDA applicant is not required to provide independent evidence to establish the safety and effectiveness of the proposed product, as is required for an NDA. Instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.

In addition to the above, an ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent[36] to the RLD, and to ensure the product's identity, strength, quality, and purity.

ANDAs for a drug-led combination product should also include sufficient information to demonstrate that the non-lead constituent part is compatible for use with the final formulation of the drug constituent part. For example, 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 the delivery device constituent part(s) of a proposed generic combination product.[37]

As a general matter, in assessing the therapeutic equivalence of a proposed generic drug-device combination, FDA will consider whether the proposed generic product can be substituted with the expectation that it will have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling.[38] While, FDA does not expect that the proposed generic combination product and its RLD 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.

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[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.

C. Biologic-led combination products

Most biological 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., a "stand-alone" BLA) or under a section 351(k) BLA for a "biosimilar" or "interchangeable" biological product.[39]

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.[40] 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.[41]

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 recombinant protein in an autoinjector

[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.

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

An abbreviated licensure pathway is available under section 351(k) of the PHS Act for products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product.[42] 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."[43] 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.

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 or dosage form; or
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved;

or otherwise does not meet the standard for biosimilarity.

[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.

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]
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[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.

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 was not applicable to the predicate product. These changes raise different questions of safety and effectiveness, precluding a meaningful comparison with the predicate product.[46] Therefore, these changes in indications for use of the product and its 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 – both the new drug indication 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. 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). Specifically, a demonstration that general and special controls provide a reasonable assurance of safety and effectiveness is sufficient to demonstrate the safety and effectiveness of the change to the drug constituent part.

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

[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).

547 and potential mitigation measures and special controls for each risk for a product such as Product
548 A.
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550 **Table 1 – Identified Risks and Potential Mitigations for Product A**
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Identified Risks	Potential Mitigation Measures	Potential Special Controls
Toxicity	▪ Biocompatibility evaluation ▪ Animal performance testing/study information ▪ Clinical data ▪ Labeling ▪ Post-market surveillance (e.g., evaluate potential drug-related toxicity in a broader population)	▪ 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) evaluation[47] 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: - 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	▪ Clinical data on effectiveness ▪ Animal study information ▪ Non-clinical bench performance testing (e.g., assays) ▪ Labeling	▪ 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	▪ Technical specifications/Technological characteristics ▪ Chemistry ▪ Stability	▪ 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.

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[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.

Example 2: *New drug indication added*

Predicate Product: Product A described above.

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 subsequently proposes a new anti-inflammatory indication for 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 its 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.

Example 3: *Different method of drug coating*

Predicate Product: Product A described above.

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 as compared to the drug coating alone that was 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.

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 drug 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 the 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. 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.

Drug Constituent Part: The same drug constituent part as 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 the 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. If the performance data fail to demonstrate substantial equivalence, or there is not compliance with the 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. 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.

Drug Constituent Part: An NDA approved drug product containing a different antimicrobial active ingredient that is 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 Antimicrobial B.

New Product: The sponsor replaces Antimicrobial A in Product A with a different antimicrobial that has also been approved in an NDA (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.[48] 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.

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 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.