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Review Article

A Guidance on Premarket Pathways for Combination Product in the United States of America

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ABSTRACT

The Office of combination products OCP, an agency to regulate the combination products under the US Food and Drug Administration (FDA) has released the final guidance on the combination products for its approval which is named "Principles of Premarket Pathways for Combination Drugs," which provides the FDA's current strategies on the approval of combination products into the market. The final guideline, which is comparable to the draft notification issued in February 2019, emphasizes and specifies the five particular instances in which those techniques apply.

Keywords: Combination products, Premarket pathway for NDA, ANDA, 510K and Denovo, etc.,

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INTRODUCTION

The final guideline is provided in January 2022 as the FDA insists to implement the 21st Century Cure Act (Cures Act), which aims at openness, efficiency, and regulatory consistency to make it simpler to manufacture safe and effective combination medicines. The guidance describes CDER, CBER, and CDRH premarket submissions for combination products, as well as the various submission techniques for each review centre and pathway.[1]

The regulation describes how the FDA works with the appropriate lead centre to evaluate premarket submissions and regulate medical components. The research offers recommendations on how to pick the most appropriate form of the premarket submission procedure for your combination product type, as well as the pathways, that are chosen depending on the major mode of action of the product (PMOA).[2]

The Final Advice, Like the Draft, Covers the Following Topics

- In 21 CFR 3.2 (e), combination products are covered.[3]
- Agency centres are assigned to combination products based on their authority.
- Approval processes for device-led, drug-led, and biologic-led combination therapy.
- Sponsors must give statistics and information on safety and efficacy, depending on the strategy.

Other significant concerns from the draft version of the advice have reappeared in the final form

- "Normally, a single usage for a combination product is suitable," but "may not be appropriate in certain cases." As a result, the USFDA is looking for feedback on when two applications should be submitted: one to the main lead agency Center and one to the non-lead agency Center."
- The FDA's OCP asks the Centers to collaborate on combination product approval applications, "including by making sure that agency components and staff cooperate appropriately on premarket evaluation of these medications, and that agency thinking is aligned in executing these reviews into the actual process." This might reflect an internal FDA perception that the Centers have not been completely coordinated in their evaluation of submissions, as well as further OCP engagement, both to promote robust participation throughout the agency and to resolve any following difficulties.

  "The data and information required to direct the safety and effectiveness query subjected to a combination product's non-lead constituent part may vary from the data and information required to obtain marketing authorization for that article as a supporting product that is not part of a combination product," the FDA expressly states, addressing an issue that may have been poorly considered and inconsistently applied.

The FDA, on the other hand, included the following details in the final guidance

- While sponsors may propose and are expected to recommend the category and/or assignment they feel should apply for a pre-RFD, OCP makes the final choice based on applicable agency components.
- "Cross-labeled combination products for which separate marketing clearance for constituent parts is sought (e.g., a new drug application (NDA) for the medicine and a premarket notification (510(k)) for the device) might provide special complications. All contacts with the FDA for these combination drugs, regardless of the feedback

asked, should take place through the lead centre before filing separate marketing authorization submissions."

- Meetings between the FDA and sponsors are attended by review staff from each centre as needed, depending on the themes and purpose of the meeting, and consulting centres complete their evaluations on time and follow the recommendations.
- The advice emphasizes the significance of recognizing combination products 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 an IND submission, investigational device exemption (IDE) submission, Q submission, 510(k) submission, premarket approval application (PMA), and/or classification request submitted under section 513(f)(2) (De Novo request).
- To speed regulatory interactions with the agency and avoid unnecessary repetition that may occur with several applications, the FDA presently feels that a single application for a combination product would be appropriate.
- When examining the relevance of the De Novo technique for such device-led combination products, one must examine one's understanding of the biological product or drug constituent parts, as well as the limitations of that information.[1]

  As defined by section 503(g) of the FD&C Act, a combination product is a medical product that combines two or more separate categories of medical products (e.g., a medicine, device, and/or biological product). and 21 CFR part 3. Combination products' constituent pieces include the drugs, equipment, and biological products that comprise the combination product.

Under 21 CFR 3.2(e), combination products are defined as follows

A product composed of two or more regulated components, such as a drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise merged or blended and created as a single entity (For example, a drug-eluting stent or a prefilled syringe);

A combination product is allocated to an Agency centre that will have primary regulatory power (i.e., leadership). The assignment of a combination product to a lead centre under section 503(g) (1) is based on determining which portion generates the combination product's primary mode of action (PMOA).[3]

If the PMOA of a device-biological product combination product is attributable to the biological product, for example, the premarket review centre for that biological product would have primary responsibility for the regulation of the combination 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 the preparation of an RFD, with input from the necessary Agency components, the Office of Combination product, if you are unsure or disagree with a centre on product classification or which centre is the lead for a particular product. The overlaps and disparities between the legal and regulatory standards applicable to the medication, device, and biological product constituent parts that make up combination products are addressed by specialized regulatory requirements for combination products.[4]

FDA "shall conduct the premarket review of any combination product under a single application, whenever appropriate," according to Sections 503(g)(1)(B) and 503(g)(6) of the FD&C Act, and a sponsor may choose to submit separate applications for each part of a combination product unless FDA "determines that a single application is necessary."[5]

To speed regulatory interactions with the Agency and avoid unnecessary repetition that may occur with several applications, the FDA presently feels that a single application for a combination product would be appropriate. For the cross-labeled combination product which contains different constituents, separate applications are permitted and applicants should coordinate with both centres (and may kindly ask OCP assistance) to help enable efficient, quick, and efficient consideration of differences that might have been relevant to each constituent part, or sometimes both, and their combined use, including modifications to either constituent part during the product lifecycle.

The marketing application type (for a device-led combination product, a PMA, De Novo, or 510(k); an NDA or ANDA for a drug-led combination product, or a BLA for a biologic-led combination product) must normally correspond to the PMOA of the combination product. To guarantee the safety and performance of a combination product in a single application, the application must also allow for an essentially identical evaluation to that applied to each constituent part individually (– for example, an ANDA or NDA for a drug as well as a PMA, De Novo, or 510(k) for such a device), which include evaluation of data and information which would be assessed individually. If a single application category (PMOA-based application type), including an ANDA, will not provide one such independent assessment for every constituent component, the combination product must usually be evaluated in an individual application type, such as an NDA, that still coincides with the PMOA of the combination product.[6]

PATHWAY AVAILABILITY AND RELATED CONSIDERATIONS

Section 3038 of the Cures Act addressed numerous issues of combination products regulation. The law, among other things, reflects and clarifies the availability of the PMA, De Novo classification, and 510(k) routes for device-led combination items.[7]

A. Device-Led Combination Products

The FDA recommends that PMA clearance for class III devices may be allowed to be marketed legally. The FDA analyses whether a PMA seems to have enough proper scientific reports to validate that the device or device-led combination product is medically beneficial for its stated function (s).[8]

Sponsors must ensure certain that PMA applications involving device-led combination products have sufficient data to demonstrate the overall safety and effectiveness of the combination product, containing information on all components (s). Technical specifications, non-clinical laboratory findings, and clinical trials are also all included in the PMA.[9] Before actually accepting or rejecting a PMA, the appropriate FDA advisory panel may convene a community meeting to assess it and make a suggestion to FDA about whether the proposal should be accepted or rejected.[10]

De Novo Classification Requests

Novel devices which have not previously been categorized or recategorized by the FDA based on the definition in section 513(a)(1) of the FD&C Act are generally classified into class III and maybe reclassified into class I or class II via the De Novo classification procedure. A sponsor may seek De Novo categorization if they feel their products are acceptable for class I or class II classification.[11]

If the sponsor demonstrates that the requirements in section 513(a)(1)(A) or (B) of the FD&C Act have been fulfilled, FDA approves the De

Novo classification request and provides a written order classifying the individual product and product category in class I or class II. If a product is classed as class II, it is granted marketing permission according to general and distinctive special controls that provide adequate assurance of safety and effectiveness.

In 510(k) submissions, such a product could be used as a legally marketed (predicate) product. If the product is unable to be classed as class I or class II, the De Novo request is rejected, and the product is designated as class III and requires PMA clearance. Special controls apply to class II products, which should offer evidence of safety and effectiveness to validate their classification. For the desired product to be classified as class II, subsequent products must be found to be approximately similar to the product that was the subject of the De Novo, and also comply with general controls and applicable special controls; non - compliance with special controls would then result in the product being categorized as class III will need PMA clearance. and requiring special controls.

Premarket Notification (510(k)) Submissions

The PMA and De Novo review standards differ from the 510(k)-review requirement (substantial equivalence of a novel product to a predicate product). Although the 510(k)-review process is equivalent, the PMA and De Novo review standards require independent confirmation of safety and effectiveness. However, in every 510(k) evaluation, the substantial equivalence finding is predicated upon safety and efficacy standards.

Section 513(i) of the FD&C Act establishes the standard for determining significant equivalence in a 510(k) review. If a product meets these criteria, it is a predicated product:

- has the same intended purpose as the product before the first one; and
- reflects the predicate product's technical characteristics

  or
- is designed to perform the same purpose as the existing version

  It features several technical characteristics.[12]

  A 510(k) submission cannot be used to eliminate the following products:
- This product's designed purpose is distinct from that of the preceding product.
- A product that distinguishes technically from the predicate product and generates unique safety and effectiveness concerns than the predicate product.

A device that is not incorporated with a drug or biological product constituent part cannot, in just about all cases, be employed as the basis for a 510(k) for such a device-led combination product. This is attributable to the reality that incorporating the pharmaceutical or biological product constituent section would very likely generate a novel intended application and/or various technical characteristics, resulting in various safety and effectiveness problems than the predicate. Additionally, a product with a separate active constituent than the predicate would have significant differences in variables such as design and materials, generating new safety and effectiveness concerns.

B. Drug-Led Combination Products

1. An NDA or ANDA is typically the right marketing authorization route for a drug-led combination product. This discussion outlines the current Agency thinking on the availability of the NDA and ANDA approaches to obtain marketing authorization for drug-led combination products.

2. **New Drug Application (NDA)**

   An NDA is typically the ideal method for drug-led combination products that aren't generic versions of already-approved drug-led combination medications.

   Under Section 505 of the FD&C Act, there are two categories of NDAs. A 505(b)(1) application, also termed a stand-alone NDA, includes extensive results of safety and effectiveness research conducted by or for the candidate, or for which the candidate has a source or use license.

   A 505(b)(2) application also includes full reports of safety and effectiveness investigations; however, at least some of the safety and effectiveness data required for approval comes from studies not conducted by or for the applicant and for which the applicant did not obtain a right of reference or use.[13]

   Section 505(b)(2) allows an authorized drug substance (or an approved drug-led combination product) to be founded on FDA safety and/or efficacy data, as well as previous studies. Instances of current drug-led combination products that are suitable for registration under section 505(j) of the FD&C Act must not be granted through the 505(b)(2) pathway (see 21 CFR 314.101(d)(9)). Section 505(b)(1) and 505(b)(2) applications are both submitted and authorized under the FD&C Act's Section 505. (c).[14]

Abbreviated New Drug Application (ANDA)

An ANDA is typically the ideal option for a drug-led combination product that has the same active constituent(s), dosage form, strength, administration route, indications of use, as well as other features (with some allowable differences)labeling as a product previously approved under section 505(c) of the FD&C Act (i.e., a reference listed drug (RLD)).[15]

ANDAs also need to provide enough data to show that the proposed product is substantially similar to the RLD.[16] Apart from ensuring product identification, potency, quality, and purity, An ANDA registrant is not needed to provide independent proof proving the safety and effectiveness of the proposed product to become eligible; instead, the ANDA is based on the FDA's conclusion that the RLD is safe and effective.

ANDAs for drug-led combination products should also include enough data to show that the non-lead component is compatible with the final formulation of the drug element component. Prospective candidates should consult relevant FDA guidance publications and other sources for information on what data and information should be provided to validate the device part(s) of a proposed generic combination product.[17]

C. Biologic-Led Combination Products

Section 351 of the Public Health Service Act (PHS Act) permits biologic-led combination medications to be licensed via one of two BLA pathways: a section 351(a) BLA (stand-alone BLA) or a section 351(k) BLA for a biosimilar or interchangeable biological product.[18]

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

Before a biological product can be licensed, it must be demonstrated to be safe, pure, and potent, and the facilities where it is generated, manufactured, packaged, or kept must comply with standards meant to keep the biological product safe, pure, and potent.[19]

A BLA filed under section 351(a) of the PHS Act is considered a stand-alone application because it includes all of the data and information necessary to establish compliance with these standards. Except for items that are meant to be biosimilar to or interchangeable with such

a previously authorized biological product, this technique is largely applicable for biologic-led combination medications.[20]

When the manufacturer does not want to depend on FDA clearance of another biological product to demonstrate biosimilarity or interchangeability, this technique is acceptable for the items listed:

- a combination of gene therapy and a specifically designed delivery catheter.
- a vaccine is given in an already loaded syringe.
- an autoinjector containing a protein product.

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

The standards for the licensing of biological products that are proved to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product is outlined in Section 351(k) of the PHS Act.

ANNEX

Analysis of Premarket Pathways Availability for Device-Led Combination Products

Illustrative Examples of the Application Part

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

Example 1: Antibacterial 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 pleural cavity for drainage of excessive fluids).

Drug Constituent Part: A hypothetical antibacterial coating (Antibacterial 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 antibacterial 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.

New Product: The sponsor proposes to add an antibacterial coating (Antibacterial 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 antibacterial drug product has never been combined with this device type. To make a substantial equivalence determination, the following questions are generally asked:

Is the predicate product legally marketed?

Yes.

Does the predicate product have the same intended use?

While both the predicate and the new combination product are intended to drain excess pleural fluid from the pleural cavity, the addition of the proposed drug constituent part and the indication of preventing infection do not apply 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 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 Antibacterial A is a different technological characteristic that would raise different questions of safety and effectiveness.

- Further, in this case, the 510(k) pathways would not allow for an evaluation substantially similar to that which would be applied to the drug constituent part under a separate application. Specifically, a 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 sections 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. If the product does not meet the requirements for the 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. 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.

Example 2: New drug indication added

Predicate Product: Product A described above, 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-viral 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 antibacterial 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 pleural fluid from the pleural cavity, the new anti-viral indication and the associated labeling regarding reducing inflammation did not apply 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 the constituent part would result in a new intended use, and the product would be found as NSE.

Further, in this case, the 510(k) pathways would not allow for an evaluation substantially similar to that which would be applied to the drug constituent part under a separate application. Specifically, a 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.

CONCLUSION

While sponsors may propose and are expected to recommend the category and/or assignment they feel should apply for a pre-RFD, OCP makes the final choice based on applicable agency components. "Cross-labeled combination products for which separate marketing clearance for constituent parts is sought (e.g., a new drug application (NDA) for the medicine and a premarket notification (510(k)) for the device) might provide special complications. All contacts with the FDA for these combination drugs, regardless of the feedback asked, should take place through the lead centre before filing separate marketing authorization submissions." Meetings between the FDA and sponsors are attended by review staff from each centre as needed, depending on the themes and purpose of the meeting, and consulting centres complete their evaluations on time and follow the recommendations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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