Combination Products Coalition

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Issue Summary: Cross-Labeled Combination Products

Within industry, as well as between industry and FDA, there is significant ambiguity regarding what constitutes a "cross-labeled" combination product, as defined in 21 C.F.R. § 3.2 (e)(3) and (4). This has and continues to hinder medical product innovation, particularly related to novel drug delivery systems, digital health products used in conjunction with drugs or biologics, mandated use of closed system transfer devices, increasing use of unconventional routes of administration, and use of devices in conjunction with orphan drugs.

Additionally, the regulatory requirements (including data required for submissions, labeling specifics, and required agreements between parties) are unclear or unknown for cross-labeled combination products.

There is also a lack of guidance on products that are not formally combination products, but make some type of reference (often, general, such as classes of devices or drugs) to other regulated medical products within labeling, which have been informally named "one-way" labeled products. The regulatory requirements for these products are also unknown, such as compatibility requirements for a drug that makes reference to general classes of delivery devices, or data requirements for software as a medical device that utilizes approved labeling of various drugs.

The Combination Products Coalition (CPC) respectfully requests guidance on this topic while taking into account considerations included herein.

Contents

Background

Cross-labeled combination products have been a topic of interest and discussion since regulation of combination products was initiated by FDA in the early 1990s, with ambiguity and concerns remaining for industry even after the creation of FDA's OCP in 2002. The CPC understands that this lack of clarity originates from the necessarily broad definition of combination products in the pertinent regulation.[1]

Public engagements on the topic have included the FDA/DIA Cross Labeling Workshop held in 2005, the Devices Referencing Drugs Workshop held in 2017, public dockets for the Product Jurisdiction Proposed Rule published in 2018, the *Principles of Premarket Pathways for Combination Products* draft guidance published in 2019, as well as a lengthy discussion at the CPC Annual Meeting on April 2, 2019 (attended by representatives from FDA OCP)[2]. Unresolved concerns in these proceedings demonstrate the continued need for clarity in this area. Such concerns include the ambiguous definition of cross-labeled combination products, inconsistent regulation of such products, and unclear regulatory pathways available for "combined use" products (defined later in this document), particularly for drugs that may wish to reference legally marketed devices, among other regulatory concerns regarding cross-labeled products that have not been addressed in guidance.

The CPC appreciates FDA's interest and continued engagement with industry on cross-labeling issues, and we understand that, within FDA, there have also been long-running internal discussions on this topic. We note that some FDA representatives have advocated for a narrow definition of cross-labeled combination products (where both products are truly "required to achieve the intended use, indication, or effect," for example, photodynamic therapy), which we support. In the past, there have also been discussions about the wording of this portion of the regulation;[3] while we are not advocating for a change in that language, we note the long-standing concerns with the ambiguity. We have had positive discussions with various FDA representatives on this topic, and believe the time is ripe to take the next step towards clarity for such products.

Our primary concerns include:

- Clarity on the **definition of cross-labeled combination products**[4] (i.e., what is and what is not a combination product) and considerations in determining if/when separate FDA-regulated products constitute a combination product, including:
    - Additional clarity on regulatory (e.g., submission data, quality system, and labeling – particularly the need for "mutually conforming labeling") requirements and expectations.

[1] 21 C.F.R. § 3.2(e)(3)-(4).
[2] Additional background content is provided in the Appendix to this document.
[3] *Id.*
[4] *Id.*

  - Additional flexibility as to when two submissions will be acceptable,[5] along with methods for accommodating review of multiple submissions for marketing authorization of the combination product.

- Clarity on **"combined use"** or "one-way labeled" FDA-regulated products that may reference another general class or specific product, but do not meet the definition of a combination product. Our interests mostly concern drug or biologic products that make reference to medical device(s). In particular, we would appreciate:

  - For "combined use" products, additional clarity on regulatory (e.g., submission data, Quality system, and labeling) requirements and expectations.

An example of success in the area of "combined use" has been companion diagnostics, where FDA developed guidance that provides a clear co-development pathway and allows for competition without formally designating them as combination products. The guidance includes clear information on coordinating submissions and regulatory expectations, and we hope that a similar level of clarity can be brought to a wider range of products.

[5] *See* 21 U.S.C. § 353(g)(6).

Impact

The ambiguities around the definition of cross-labeled combination products have hindered development of innovative products as developers are unsure of the regulatory requirements for such products, and therefore the costs associated with development programs. These costs may or may not include clinical trials, combination product development (under design controls), stability studies, partnerships with other manufacturers, or customized products designed for a specific need, with those requirements very much depending on the regulatory pathway.

Additionally, there are known to have been review delays and inconsistencies specifically due to cross-labeling issues, particularly for devices that are used to deliver certain drugs. This creates a significant concern for drug and biologic manufacturers who instead prefer to avoid such delays by specifically not proceeding with devices that may be considered combination products, thereby hampering innovation across the industry.

As described in further detail below, areas of particular concern include: (i) orphan drugs for rare diseases; (ii) delivery devices for novel therapies via unconventional routes of administration; (iii) closed-system transfer devices for certain classes of drugs; (iv) regulated digital health products used in conjunction with drugs and biologics; (v) insulin delivery systems; and (vi) "combined use" products (that are not formally combination products, but whose labeling have some type of reference to another type of FDA-regulated product), including "combined use" within a clinical trial.

To start, we note that manufacturers of orphan drugs face significant burdens due to lack of corresponding incentives for device manufacturers to cooperate with specialized devices to accompany such drug or biologic products. Often, device manufacturers are unwilling to work with drug or biologic manufacturers for low-volume products (often the case for orphan/rare diseases). Although not exclusively the issue, consider the difference in the statutory definitions of orphan drugs (i.e., those intended for the treatment, prevention, or diagnosis of a disease or condition affecting less than 200,000 patients in the U.S.) versus humanitarian use devices (i.e., those intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the U.S. per year). Drug and biologic manufacturers have little recourse when device manufacturers are unwilling to cooperate, specifically when FDA determines the setup to be a cross-labeled combination product.

Furthermore, multiple novel drugs and biologics require unconventional routes of administration in order to optimally target specific physiological locations, including bypassing the blood-brain barrier (e.g., in the case of the intrathecal and intracerebroventricular routes, but also various modes of ophthalmic delivery). This has provided a mechanism to give hope to patients with previously untreatable diseases. Unfortunately, there are few (and in some cases, no) delivery device options in some of these areas, adding to the development costs and timelines, with the possibility of a product being considered a cross-labeled combination product a substantial concern through development.

Other concerns exist as well, including mandated use of closed-system transfer devices under compendial requirements, and the fast-growing digital health market that both industry and regulators have recognized as important. The ability of industry to clearly understand the classification of products and how they are regulated is essential for advancing product development to treat new diseases and improve treatments in others.

Finally, "combined use"[6] products have been held to different standards based on the center within FDA responsible for regulation, time of approval (as such products have existed for some time, particularly in the case of insulin delivery devices), the review Division, and similar/predicate/reference products that may have preceded a given product. Given the increasing number and prevalence of drug delivery devices and drugs administered via such devices (for instance, biologic drugs administered via intravenous or subcutaneous routes of administration), there are an increasing number of "combined use" scenarios where such products can be used within the intended use of each other. Additionally, we would like to note inconsistencies during review of clinical submissions where there is "combined use" (for instance, an IND referencing medical devices used to prepare or administer the investigational drug or biologic) and would like to understand when we can rely on the status of legally marketed products (e.g., when a product is used within its cleared/approved indication) or when a right of reference is required. We are particularly interested in the regulation of "combined use" products, given a historically narrow definition of cross-labeled combination products, and believe there is a significant opportunity for clarity on this topic.

[6] Products that are not formally combination products, but have some type of reference to another type of FDA-regulated product within labeling.

Request for Guidance and Considerations

The CPC respectfully requests guidance from FDA to clarify the following aspects of cross-labeled combination products and "combined use" products. We have provided this document to inform such a potential guidance, noting that this has not been agreed to by FDA but we hope can facilitate future discussions on the topic.

Note that the main topic areas (**in bold**) are intended to be covered in the proposed guidance, while sub-bullets provide further detail as well as industry (CPC) preference but are subject to change or negotiation. Some notes not intended for inclusion in a future guidance are boxed. We recommend inclusion of example(s), potentially including both a cross-labeled combination product as well as a "combined use" scenario to demonstrate application of the concepts described in said guidance; we have provided examples of different categories of cross-labeled or "combined use" products in a separate document.

We would like to highlight item **1.d** that focuses on the "Companion Diagnostic approach" which allows some level of regulatory flexibility in bringing new "combined use" products to market while balancing the need to link the products together to some degree (particularly in cases where both products need to be brought to market in parallel).

1. **Definition of Cross-Labeled Combination Products**
   Clarity on the definition of cross-labeled combination products (i.e. what is and what is not a cross-labeled combination product) and considerations in determining if/when separate FDA-regulated products constitute a combination product[7].
   a. Recognition of a narrow definition of cross-labeled combination products (where both products are "required to achieve the intended use, indication, or effect," where the labeling of both products are required to specifically reference each other (i.e. each product is not designed and/or intended to be used with other drugs/devices/biologics besides that/those with which it is cross-labeled) to ensure their safe and effective use together, photodynamic therapy (Visudyne) being the most prominent example referenced by FDA). This has been stated by FDA representatives, including in the preamble to the original publication of 21 C.F.R. § 3[8], which we support. A thorough explanation of this portion of the regulation would be valuable for the purpose of this guidance.
      i. For products that do not meet such a narrow definition, we would encourage a clear definition be established and common terminology utilized. Recently, the use of FDA-regulated products of different types together that do not meet the definition of a cross-labeled combination product has been termed "combined use" but has also been called "one-way" labeling, "concomitant use," or "mutually conforming labeling." We are treating these terms as synonymous but would prefer to establish a common term with a clear

[7] 21 C.F.R. § 3.2(e)(3),(4)
[8] 56 FR 58756, November 21, 1991, which includes the following within the preamble: "Thus, the definition of a combination product is intended to exclude most concomitant use of drugs, devices, and biological products."

definition, as such "combined use" is relatively common and poses questions that member companies must address, such as data required in filings and labeling content. We note that such products are not a "combination product" (in accordance with FDA's statutory definition) and, therefore, would not follow combination product regulations. This topic is explored further in Section 2 of this document.

ii. Other types of combination products (single-entity and co-packaged, as described in 21 C.F.R. § 3.2(e)(1) and (2), respectively) are *not* within the scope of this document, as we believe their definitions are, in general, sufficiently clear.

b. We believe cross-labeled combination products are those designed and tested to specifically work together to achieve the clinical effect and could *not* have the intended effect if used with anything other than the *uniquely specified* constituent part(s).

NOTE: We have experienced a lack of certainty regarding the designation of cross-labeled combination products and would, ideally, like formal processes to align consistently with FDA on such matters, along with information (e.g., guidance) to allow us to independently prepare for such a decision in a predictable manner. It would be helpful to get to an understanding where products are not cross-labeled combination products unless explicitly agreed and determined by FDA (OCP), and in what forum such a decision would be made. We would like flexibility in the type of forum for having such discussions, realizing that these may occur under a forum run by the Office of Combination Products (RFD, pre-RFD) or at center-specific meetings or engagements (e.g. Type A/B/C meetings with CDER, Q-sub meetings with CDRH, INTERACT meetings with CBER, etc.) that would include input from OCP. We also note that such a designation has a significant level of impact on our programs, both from a procedural perspective (such as identification of combination products in FDA Forms 1571 and 356h, determination of applicable postmarket safety reporting requirements per 21 C.F.R. 4 subpart B) and from a product development perspective (such as the determination of when and how products must be studied together clinically). Additional predictability and certainty would reduce the number of regulatory questions and development risks, and help facilitate the study and approval of innovative products.

c. Additionally, just because certain products are studied together clinically does not automatically determine their regulatory status as a cross-labeled combination product if they do not otherwise meet the preceding criteria (i.e. if they are both required to achieve the intended effect).

NOTE: We have observed some situations where companies may elect to have "one way" labeling for the convenience of patients/users in a "combined use" scenario. Although this does not meet the definition of a combination product, it is sometimes treated as such by FDA. We believe that flexibility should be allowed for various reasons, including convenience, but that referencing other products within one product's labeling should not be the sole driving factor behind designation as a combination product (see the Pulmozyme example in the accompanying *Examples* document).

d. We would desire flexibility in the regulation of "combined use" products, and other regulatory constructs exist that may be able to facilitate such flexibility. We note there are some situations

where approvals of multiple products is required on the "first time through" where neither constituent exists or is labeled in its current form and require some form of codevelopment or mutual labeling, akin to Companion Diagnostics as described in the draft guidance *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product*[9]. We note that per this draft guidance, Companion Diagnostics are not considered combination products with the therapeutic products for which they are associated, and this allows follow-on diagnostics to come to market after initial approval(s), with FDA updating the list of associations on their Companion Diagnostics webpage[10]. While Companion Diagnostics present unique concerns and are heavily weighted towards oncology indications, similar concepts may apply to other combined use scenarios rather than strictly following the cross-labeled combination product construct.

i. We acknowledge that timing of the availability of products is an important factor in the case of "combined use" determinations, particularly if one or both products are investigational or if the products are not appropriately labeled for use together. The Companion Diagnostic framework is useful in that it allows for codevelopment without overly tying the products together from a regulatory standpoint and provides clarity on the steps involved. Although "combined use" products are different from Companion Diagnostics, this framework captures the spirit of how to allow flexibility for co-development without being overly restrictive. The spirit of this framework also provides a pathway for future changes without requiring updates to labeling.

ii. We support other frameworks besides a formally designated cross-labeled combination product when at all possible to allow for flexibility on behalf of sponsors and FDA. Such constructs are discussed later in the "combined use" section of this document.

iii. Such alternative frameworks will allow for various types of relationships between different sponsors/manufacturers, per their business objectives, and will also more readily facilitate generic/biosimilar/follow-on competition, which has been a clear objective of FDA.

NOTE: With the "Companion Diagnostic" approach, we appreciate the flexibility in the labeling whereby the products do not need to be specifically tied to each other, which also allows various types of business relationships between sponsors and also allows for future changes without overburdening one party or another. We hope that such attributes could be applied to other frameworks.

e. Clarification of specific product attributes that contribute to status as cross-labeled combination products, including those specifically referenced in the CDER-CDRH Intercenter Agreement[11]: indications, general mode of delivery, and drug dosage/schedule requirements. These would include those specific attributes that are specified in the regulation where "upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to

[9] https://www.fda.gov/media/99030/download
[10] https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools
[11] https://www.fda.gov/combination-products/classification-and-jurisdictional-information/intercenter-agreement-between-center-drug-evaluation-and-research-and-center-devices-and

reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose." Additionally, it would be helpful to obtain clarity regarding other attributes such as in our examples of cross-labeled combination products[12], where use together presents new questions of safety or efficacy.

i. A graphical flow diagram (decision tree) would be a useful tool within guidance to step through the process of determining of "combined use" products meet the narrow definition of a cross-labeled combination product.

f. It would also be helpful to obtain clarity related to 21 C.F.R. § 3.2(e)(4) concerning investigational products used together, particularly when one investigational product is used in conjunction with a *legally marketed* device (within its intended use), and if, combined with subpart 3, what would constitute a *required* (not desired) "change" in its indication/labeling that would create a combination product. We desire all scenarios to be sufficiently covered in potential guidance for clarity (i.e. combinations of investigational/marketed products with consideration for drugs/biologics/devices).

g. We do understand that products used together in an investigational setting may not represent the eventual commercial use of the products, and some flexibility during clinical investigations may be warranted. Clearer definitions and expectations in this area will assist sponsors in ensuring the right level of information is collected and provided to FDA at the right time, either during clinical or commercial filings, or that questions can be posed to the agency to prepare for such filings.

NOTE: Industry has experienced designation as a cross-labeled combination product sometimes having an adverse effect on the sponsor's development program as well as eventual marketing application(s). This may be due to regulatory uncertainty and the potential for lack of cooperation from the other constituent manufacturer, often driven by differing business objectives. We believe a clarified narrow definition will significantly reduce such concerns.

2. **Regulatory Requirements for Cross-Labeled Combination Products**

a. Additional clarity on regulatory (e.g. submission data and labeling) requirements and expectations for cross-labeled combination products.

i. The baseline expectation that clinical data is required to demonstrate that the products, when used together, achieve the safe and effective intended use, indication, or effect. Explanation of the level of such clinical data would be useful, acknowledging some level of regulatory flexibility.

Regardless of the formal designation of a given set of products, establishing the regulatory expectations (i.e., data required for a submission and labeling content) is necessary and is currently not defined for many situations.

ii. Additionally, aspects of combination products critical to include in marketing application(s) should be described, such as compatibility testing, adequate directions of use for each

[12] Reference the accompanying document titled *Combination Product Cross-Labeling Examples* where four categories of "combined use" products are defined: I. generic referencing (not a combination product), II. one-way labeling (not a combination product), III. Cross-labeled combination products, and IV. Products marketed under an application of a different product type.

constituent inclusive of all other constituents, any relationship(s) required between constituent part applicants outside of those described in Postmarketing Safety reporting regulations,[13] and other critical information.

iii. We note that there are opportunities for utilizing information regarding known interactive effects between two products to establish "essential parameters" that must be considered when using two products together that could more readily facilitate "combined use." While such information is established on a case-by-case basis, guidance on determining such parameters and how that would impact labeling would facilitate development. Finally, such a scenario could more readily facilitate the introduction of generics/biosimilars/follow-on products versus opaque referencing of brand names or the like.

Note: Examples of this approach are included in the accompanying *Examples* document, particularly Blincyto and Brineura (for the 'alternative' pump requirements).

i. Additional **flexibility as to when two submissions will be acceptable**[14] (as well as specific instances with justifications as to when two submissions will not be acceptable), along with methods for accommodating review of multiple submissions for marketing authorization of the combination product. Note that this only applies to formally designated cross-labeled combination products, since other "combined use" products must allow for separate marketing authorization.

i. We note that FDA has a stated preference for a single application, as described in the *Premarket Pathways* draft guidance[15]. However drug and device manufacturers may separately have a variety of scientific or business reasons to pursue separate applications, as allowed under the current statute. Such reasons may be driven by intellectual property ownership, logistical concerns, manufacturing or technical expertise, or contractual/licensing matters. We ask for flexibility in the number of types of applications to allow for various types of relationships, but further explanation of scenarios in which either a single application or multiple applications would be required. Outside of specific scenarios, we believe the existing statute and regulations provide for multiple submission pathways for some types of combination products. We also believe sufficient evidence for safe and effective use of both constituents can generally be provided in multiple applications.

For instance, an example from the referenced example document includes Prialt & SynchroMed II which are cross-labeled combination products and are approved under a separate NDA and PMA, respectively. Additionally, the previously mentioned photodynamic therapy is approved under a separate NDA and 2 PMAs (given 2 different laser brands manufactured by partner companies). These examples are more fully described in the accompanying document.

[13] 21 C.F.R. § 4.103
[14] 21 U.S.C. § 353(g)(6)
[15] https://www.fda.gov/media/119958/download

NOTE: We do not view the number of types of products referenced in a "combined use" scenario as a determining factor as to whether they are considered combination products or not, despite the language in 21 C.F.R. § 3.2(e)(3) and (4). Instead, the *necessity* for both products to be used together, as described earlier, is the critical factor, and there may be multiple options available for one (or both) of those products. For instance, multiple generic drugs or biosimilars may be marketed that could be substituted, or multiple devices that may be considered substantially equivalent.

ii. Although FDA prefers that applicants/constituent manufacturers work together as described in the *Premarket Pathways* draft guidance, we note that may not always occur, due to different business objectives, competition, etc. We believe that while working together can be encouraged, the pathways should be flexible enough to allow for different constructs, which will also help foster competition, particularly in situations when generic/biosimilar drugs/biologics or competing devices within the same product code are involved.

iii. There are situations where another type of regulated product is required to be approved within a single application from a center that does not typically evaluate such products. For instance, a medical device being provided separate from a drug or biologic (but designed for use with the drug/biologic) that is not independently marketed (but also does not constitute a single-entity or co-packaged combination product) that is approved within a drug or biologic application (NDA, ANDA, or BLA) and reviewed by CDER or CBER. We note that inclusion of two physically separate (non-single-entity) and non-co-packaged products within one marketing submission does not necessarily create a combination product. Members of industry have experienced this on different occasions, which is often driven by review divisions within the various centers. We understand that such situations are not prohibited by statute, however, industry would prefer the stated flexibility to submit within multiple applications, at the discretion of the applicant. This may still constitute a cross-labeled combination product, however the flexibility afforded by a separate application (for instance, a 510(k) for the device of concern) may be particularly useful for the applicant and is seemingly allowed by the applicable *Cures* provision.

1. If the applicant chooses a single submission and includes information for a different product type within the application (e.g. device information within the CTD of a NDA, ANDA, or BLA), it is not clear how to structure such information within a submission. For instance, the eCTD Technical Conformance Guide[16] does include information on device elements of a combination product but is not clear how to provide the equivalent of a complete device submission within the CTD structure per this scenario.

Examples are discussed in the accompanying document.

3. **Defining "Combined Use"**

Clarity on "combined use," "one-way labeled," concomitant use, or mutually conforming labeling of FDA-regulated products that may reference another general class or specific product but do not

[16] https://www.fda.gov/media/93818/download

meet the definition of a combination product (categories I and II described earlier, or generic referencing and one-way labeling, respectively). Particularly, additional clarity on regulatory (e.g. submission data and labeling) requirements and expectations. Note that in this case, there are necessarily two submissions as they do not constitute a combination product and are independently marketed.

a. Requirements and expectations for products that make *generic* reference to another FDA-regulated product, such as to a general type of device (i.e. product code or description), a class or type of drug/biologic, or a generic drug/biosimilar. This could also include an exclusionary description, such as a device that cannot be used with certain types of drugs (i.e. cytotoxic drugs), as this would provide limitations on "combined use."
b. Requirements and expectations for products that make *specific* reference to another FDA-regulated product, such as a brand or nonproprietary name of a drug, brand/model of device, etc.
c. For "combined use" that includes either generic or specific reference to another FDA-regulated product, the expectation is that the referenced product is being used within its intended use, and that there is sufficient justification to support the reference within the labeling. This justification may be based on various types of scientifically-valid data, not necessarily clinical evidence. For instance, this could be justified via in vitro testing (e.g. drug-device compatibility testing, dose accuracy testing), in vivo testing, engineering justification (e.g. tolerance analysis, material assessment), etc. In this way, the combined use of a device referenced in approved drug labeling (generically described or listed by device brand name), could be treated as a "performance claim" supported by the scientific data (also termed "essential performance requirements" in some situations, see description of infusion pumps used to administer Brineura in the accompanying *Examples* document).
    i. Some level of guidance for such data in common situations would be useful, for instance compatibility testing that would be required for an intravenous drug provided in a vial and to be used with various intravenous access devices and/or pumps. In this case, an uncertainty would be the number of devices with which to test, given the potentially significant number of devices on the market and the fact that the drug sponsor has no control over the device market (e.g. market withdrawals and/or new entrants).
    ii. An additional example would be, conversely, an intravenous access set that is labeled for general use. The preferred level of information to be provided, both in the marketing application and in the product labeling, should be described. We note that this varies for currently marketed drugs and devices.
d. For FDA-regulated products that are likely to be utilized in "combined use" applications, sufficient information regarding the product should be made publicly available to allow sufficient justification of "combined use" for other FDA-regulated products.
e. For example:
    i. An intravenous drug provided in a vial and to be used with various intravenous access devices and/or pumps is required to include the names of all inactive ingredients in the

product label.[17] This allows a manufacturer of such intravenous devices to assess or test compatibility with such drug(s). Existing regulations should sufficiently provide for this.

ii. An intravenous access device should include drug-contacting materials of construction in either the device labeling and/or a publicly available location, such as a 510(k) summary for such product. This would allow an intravenous drug manufacturer to assess or test compatibility with such device(s).

4. We understand that due to the prevalence of cross-labeled combination and "combined use" products that have a variety of approaches to labeling, there is a need to **grandfather** existing legally marketed products and that this guidance would be prospective in nature.

Additional notes:

- NOTE: The guidance construct allows for such flexibility and would be highly beneficial to industry as to not disrupt the regulation of currently marketed products while still providing clarity for products under development.
- NOTE: We understand that FDA needs to allow for fair competition under the construct of such a guidance, including provisions for generics and biosimilars, in particular (along with competitive devices of the same product code). We believe that a guidance could support such competition, specifically by providing a narrow definition of cross-labeled combination products, being more prescriptive about language necessary to include in product labeling, and allowing flexibility in approaches including the relationship between applicants.
- NOTE: Additionally, industry believes that considerations described within this document should be perceived as firmly establishing the status quo and ensuring consistency rather than disrupting existing regulatory mechanisms.
- NOTE: We believe there are benefits to both industry and FDA by establishing guidance on this topic by providing transparent definitions and ensuring consistency across both product types and the agency.

[17] 21 C.F.R. §201.100(b)(5)

Cross-Labeling and Combined Use Examples

The purpose of this section is to illustrate with specific publicly available examples following four categories of "combined use" products to facilitated discussion on the "combined use" topic (as the majority of CPC member companies are drug or biologic manufacturers, we focus on drugs or biologics that reference a medical device[18]):

I. Generic referencing (not a combination product): Drug (or biologic) generically referring to the use of one or more existing medical device(s) legally marketed for an indication consistent with its use with the drug (or biologic); technical selection criteria for the devices may be provided. Device(s) are labeled for "general use" or with a class of multiple drugs and would typically not reference an individual drug (or biologic) name or brand.

II. One-way labeling (not a combination product): Drug (or biologic) referring to the use of one or more existing medical device(s) legally marketed for an indication consistent with its use with the drug (or biologic), listing specific option(s) by brand name. Many device(s) are labeled for "general use" or with a class of multiple drugs and would typically not reference an individual drug (or biologic) name or brand, although there are some exceptions to that (some of which appear in this document).

III. Cross-labeled combination products: Drug (or biologic) referring in its labeling or investigational plan to use of a medical device by brand name as the only suitable medical device without which of the drug (or biologic) is not able to achieve its intended use, indication, or effect. The medical device specifies in its labeling that the medical device is meant to be used with the drug (or biologic) in question and would not achieve an intended use, indication, or effect absent the specified drug(s) or biologic(s). Only this category meets the definition of 21 C.F.R. 3.2(e)(3) or (4), which is (with *emphasis* added):

> (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product *where both are required to achieve the intended use*, *indication, or effect* and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
> (4) 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*.

[18] Additionally, while we provide references to NDA/BLA ("innovator") examples, we recognized that the same principles may apply to generic or biosimilar applicants (e.g. ANDA or 351(k) submissions). We do not explore topics specific to such applications in this document.

IV. Products marketed under an application of a different product type: Device being provided separate from a drug or biologic (but designed for use with the drug/biologic) that is not independently marketed (but also does not constitute a single-entity or co-packaged combination product) that is approved within a drug or biologic application (NDA, ANDA, or BLA) and reviewed by CDER or CBER.

The list of examples is not exhaustive, and is not meant to refer to issues that may possibly have been raised during the respective product reviews or during post-marketing. The products listed were selected because they present the attributes of the type of products that we would like to discuss. Again, we note that these are focused on drugs or biologics that reference a medical device. Finally, we acknowledge that there are many unique circumstances that prevent individual examples from being optimal precedents, and these are provided for discussion purposes only, not to serve as a desired future state. This list is meant to be read in the context of the preceding section (*Request for Guidance and Considerations*).

We also recognize the desire for sponsors to have regulatory flexibility in terms of the number of applications to support "combined use" products, and, therefore, we propose that all of the categories described above would allow for multiple submissions of the different types of "combined use" products. In fact, for categories I and II (generic referencing or one-way labeling), they would necessarily be submitted in separate applications.

Sponsors may utilize different labeling approaches on how the other "combined use" product is referenced (generic reference, or one-way labeling: single or multiple). We appreciate the flexibility in the different approaches, but there is lack of clarity in the type of data required for each "combined use" product (drug and device), and expectations on information to be included in labeling and/or publicly available information for each product. Additionally, what data is required within the submission and with which products (for either generic referencing or one-way labeling) is the most common source of uncertainty for sponsors. Reference the preceding sections for further detail of this uncertainty.

<u>How to read the table:</u>

> The manner in which the drug (biologic) label refers to (a) medical device(s) is shown with each example product. Generally, sections of the PI related to Dosage and Administration contain the applicable content.
>
> The last column (Data typically expected to be provided in BLA/NDA for this type of product) is a general suggestion; further description is provided in the preceding section (*Request for Guidance and Considerations*).

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
I. Generic referencing	Remicade	Janssen	BLA 103772	label	HCP	IV	• A syringe equipped with a 21-gauge or smaller needle must be used for reconstitution • The infusion must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size 1.2 um or less)	CTD Section 3.2.P.2.6: test results for compatibility drug-device, focusing on general materials of construction for drug product contacting surfaces.
	Blincyto	Amgen	BLA 125557	label	HCP	IV	• Infusion bags/pump cassettes must be of polyolefin, PVC DEHP-free, or EVA • IV tubing sets must be of polyolefin, PVC DEHP-free, or EVA • DEHP construction material is non-compatible with the product.	
	Herceptin	Roche/ Genentech	BLA 103792	label	HCP	IV	• A sterile syringe must be used for reconstitution • An infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP is to be used for infusion. Dextrose (5%) solution should not be used.	
	Kadcyla	Roche/ Genentech	BLA 125427	label	HCP	IV	• A sterile syringe must be used for reconstitution • An infusion bag containing 250 mL of 0.9% Sodium Chloride Injection is	

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
							to be used for infusion. Dextrose (5%) solution should not be used. • Administer with a 0.2 or 0.22 micron in-line PES filter.	
	Tysabri	Biogen	BLA 125104	label	HCP	IV	• Infuse TYSABRI 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP, over approximately one hour (infusion rate approximately 5 mg per minute). Do not administer TYSABRI as an intravenous push or bolus injection. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.[19]	
	Insulins (generally)	-	-	-	Patient/ caregiver	SC	• Drug: an insulin pump (criteria?) must be used for administration • The insulin pumps are for SC administration of a specified generic type of insulin	
	Fiasp	Novo Nordisk	NDA 208751	label	Patient/ caregiver	SC or IV	• Bolus injection: syringe (implicit from IFU) • Or continuous injection with insulin pump	

[19] This is an example of an "implicit" reference as no medical device is described (generically or specifically) within the label, however a medical device is required to administer the product (in this case, an intravenous infusion pump and accessories such as an administration set).

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
	Spinraza	Biogen	NDA 209531	label	HCP	Intrathecal	• Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle	
II. One-way labeling	Pulmozyme	Roche/ Genentech	BLA 103532	Drug: Label Device Label	Patient		• Drug: Administer using **eRapid Nebulizer Sytem**, or via a jet nebulizer connected to an air compressor with an adequate air flow and equipped with a mouthpiece or suitable mask (several examples given by brandname) • Device eRapid Nebulizer System: It to be used with patients for whom doctors have prescribed medication for nebulization.	CTD Section 3.2.P.2.6: test results for compatibility drug-device, with specific devices tested.
	Brineura	BioMarin	BLA 761052	label	HCP	Intra-ventricular	• Brineura is administered into the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). Brineura is intended to be administered via the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman® Ventricular Catheter (Part Number: 82-1650). The intraventricular access device	

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
							must be implanted prior to the first infusion. It is recommended that the first dose be administered at least 5 to 7 days after device implantation. • Brineura is intended to be administered with the B Braun Perfusor® Space Infusion Pump System (Product Code: 8713030). If an alternative pump must be used, the essential performance requirements for a syringe pump used to deliver Brineura are as follows: o Delivery rate of 2.5 mL/hr with delivery accuracy of +/- 1 mL/hr o Compatible with 20 mL syringes provided in the Administration Kit for use with Brineura o Occlusion alarm setting to ≤ 281 mm Hg o Cleared for intraventricular route of administration • Administer Brineura and the Intraventricular Electrolytes using the provided Administration Kit for use with Brineura components [see	

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
							How Supplied/Storage and Handling (16)].	
	Immunoglobulin G (Igg) Infusion System	EMED Technologies	510(k) K173783	label	Patient	SC	The SCIg60 Infusion System is intended for use in the home or hospital environment for the subcutaneous infusion of Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid (manufactured by CSL Behring), Gammagard Liquid, Immune Globulin Infusion (Human) 10% (manufactured by Baxalta), and Cuvitru Immune Globulin Infusion (Human) 20% (manufactured by Baxalta) with the BD 60 ml syringe (model no. 309653).	
	Syringe Agrip for the AVONEX Pre-filled syringe[20]	Biogen	510(k) K042314	summary	Patient	Intramuscular	The Syringe Grip for the AVONEX prefilled syringe is a reusable device indicated for use by the patient to assist with the self-administrered injection of a fixed dose of AVONEX from a prefilled syringe through a single lumen hypodermic needle. The devices are intended to be used in any setting including the home	

[20] No longer actively marketed by the sponsor.

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
	Invisiject Reusable Auto-Injector[20]	Biogen	510(k) K032425	summary	Patient	Intramuscular	The Invisiject Reusable Auto-Injector is a reusable device indicated for use by the patient to assist with the self-administered injection of a fixed dose of AVONEX from a pre-filled syringe through a single lumen hypodermic needle. The auto-injectors are intended to be used in any setting including the home.	
III. Cross-labeled combination product	Prialt & SynchroMed II	Tersera	NDA 021060	label	HCP	Intrathecal	PRIALT is intended for intrathecal delivery using the Medtronic SynchroMed® II Infusion System and CADD-Micro Ambulatory Infusion Pump [see Warnings and Precautions (5.2)]. Refer to the manufacturer's manual for specific instructions and precautions for programming the microinfusion device and/or refilling the reservoir. Medtronic Synchromed II indication includes: The chronic intrathecal infusion of Prialt® (preservative-free ziconotide	The cross-labeled combination products were studied together in clinical trial(s) and contain significant combined information on both constituents in the submission(s), including clinical data.

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
							sterile solution) for the management of severe chronic pain.	
	Visudyne & Visulas	Valeant	NDA 021119	label	HCP	IV	A course of VISUDYNE (verteporfin for injection) therapy is a two-step process requiring administration of both drug and light. The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with light from a nonthermal diode laser. The following laser systems have been tested for compatibility with VISUDYNE and are approved for delivery of a stable power output at a wavelength of 689±3 nm: Coherent Opal Photoactivator laser console and modified Coherent LaserLink adapter,	

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
							manufactured by Lumenis, Inc., 2400 Condensa Street, Santa Clara, CA 95051-0901, Zeiss VISULAS 690s laser and VISULINK® PDT adapter manufactured by Carl Zeiss Meditec Inc., 5160 Hacienda Drive, Dublin, CA 94568, Ceralas I laser system and Ceralink Slit Lamp Adapter manufactured by Biolitec Inc., 515 Shaker Road, East Longmeadow, MA 01028, Quantel Activis laser console and the ZSL30 ACT™, ZSL120 ACT™ and HSBMBQ ACT™ slit lamp adapters distributed by Quantel Medical, 601 Haggerty Lane, Bozeman, MT 59715	
IV. Products marketed under an application of a	Avostartgrip	Biogen	BLA 103628	label	Patient/caregiver	Intramuscular	An AVOSTARTGRIP kit containing 3 titration devices can be used for	Sufficient information to support the type of product is expected

Type of product	Name of product	Company	Application #	Link to label	Type of user	Route of admin.	Manner in which drug label refers to (a) medical device(s) (and vice versa)	Data typically expected to be provided in BLA/NDA for this type of product
different product type							titration and is to be used only with AVONEX Prefilled Syringes.	to be contained within the other type of submission (i.e. device submission typically expected within a 510(k) is expected to be contained within the CTD of the NDA/ANDA/BLA)

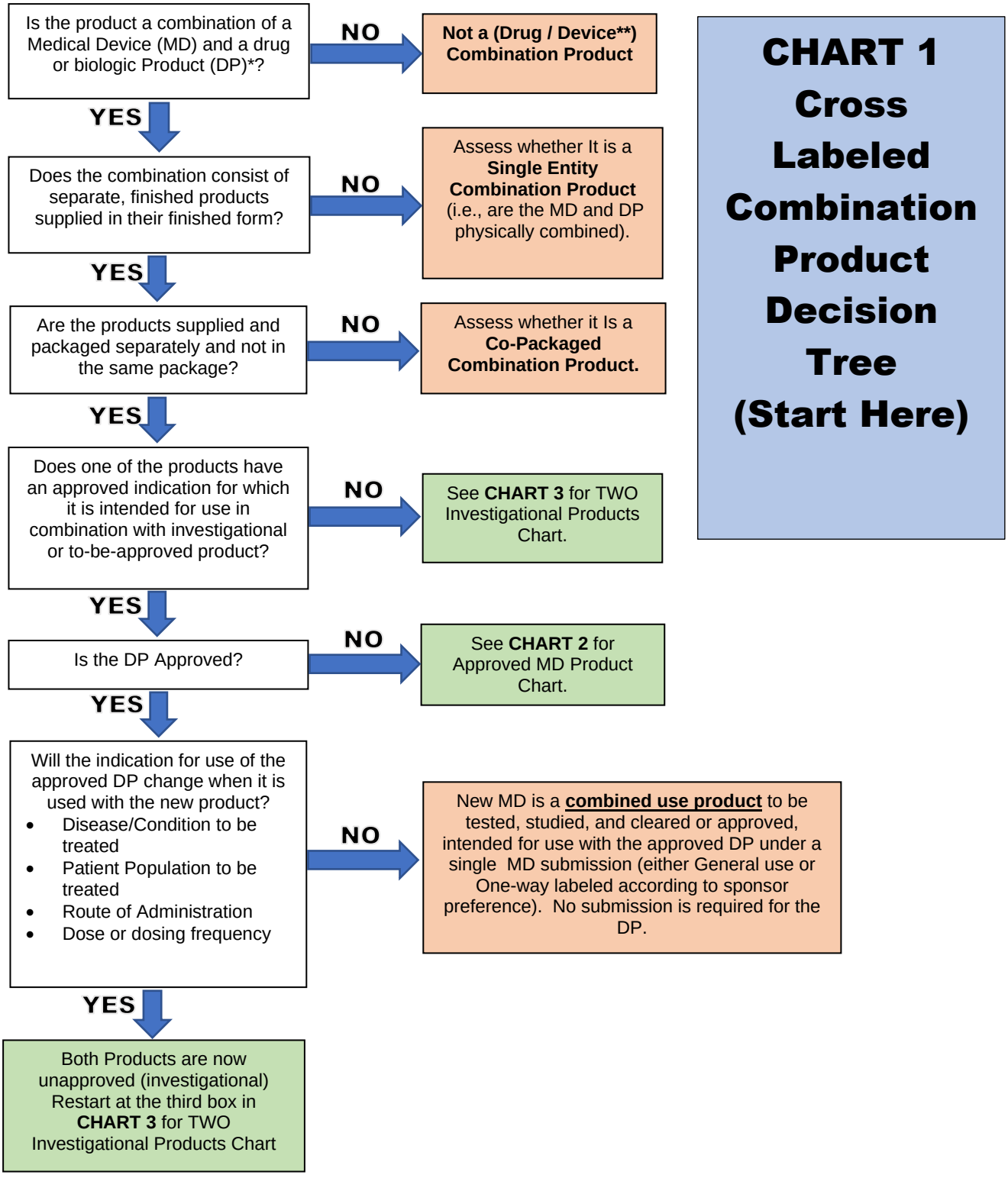
Flow Chart (Decision Tree)

CPC has developed the following flow chart (decision tree) to accompany this paper, consistent with the guidance considerations described earlier.

Note that there are three charts:

1. Cross-Labeled Combination Product Decision Tree (start on this page)
2. Approved Medical Device Decision Tree
3. Two Investigational Products Decision Tree

These flow charts appear on the pages that follow.



*Although not specifically considered in these slides, biologic/device or drug/device/biologic combination products may follow the same decision flow. Drugs and biologics are referenced as 'DP' (drug product) within this decision flow.
**Drug/biologic combination products are not explicitly considered within these flow charts.

CHART 2
Approved Medical Device Decision Tree

Is one of the finished products (MD or DP) already cleared/approved for the indication for which it will be used with the new (investigational or to be cleared/approved) combination?

NO → See CHART 3 for TWO Investigational Products Chart

YES

Is the MD Cleared/Approved?

NO → See CHART 1 for APPROVED DP Product

YES

Can the DP only be used with this MD and not available in another form (e.g. vial or PFS)
OR
Cannot be used with other commercially cleared/approved MD with a similar or broader indication?

NO → New DP is a **combined use product** to be tested, studied and approved under an NDA/BLA or supplement for use with MD specified by brand (one-way labeled), specification (characteristics) or by MD labeled for use with this product DP. (according to sponsor preference or specifics of the use case)*

YES

Indication Change?

Will this new combination change the indication for use of the MD?
E.G., New specific route of administration (i.e. inter-tumoral, intrathecal, ICV, IV, Subcutaneous, Intramuscular, intradermal, nasal, inhalations, etc.)
[NOTE: Use of the MD to deliver what is at this time an "unapproved" DP would not be considered a change in indication or intended use.]

Design Change?

Will the device require significant technological changes including new delivery technology, new functions or features; significant engineering or material changes to make it "compatible" with the unapproved DP that will make it unique for the use with this DP?

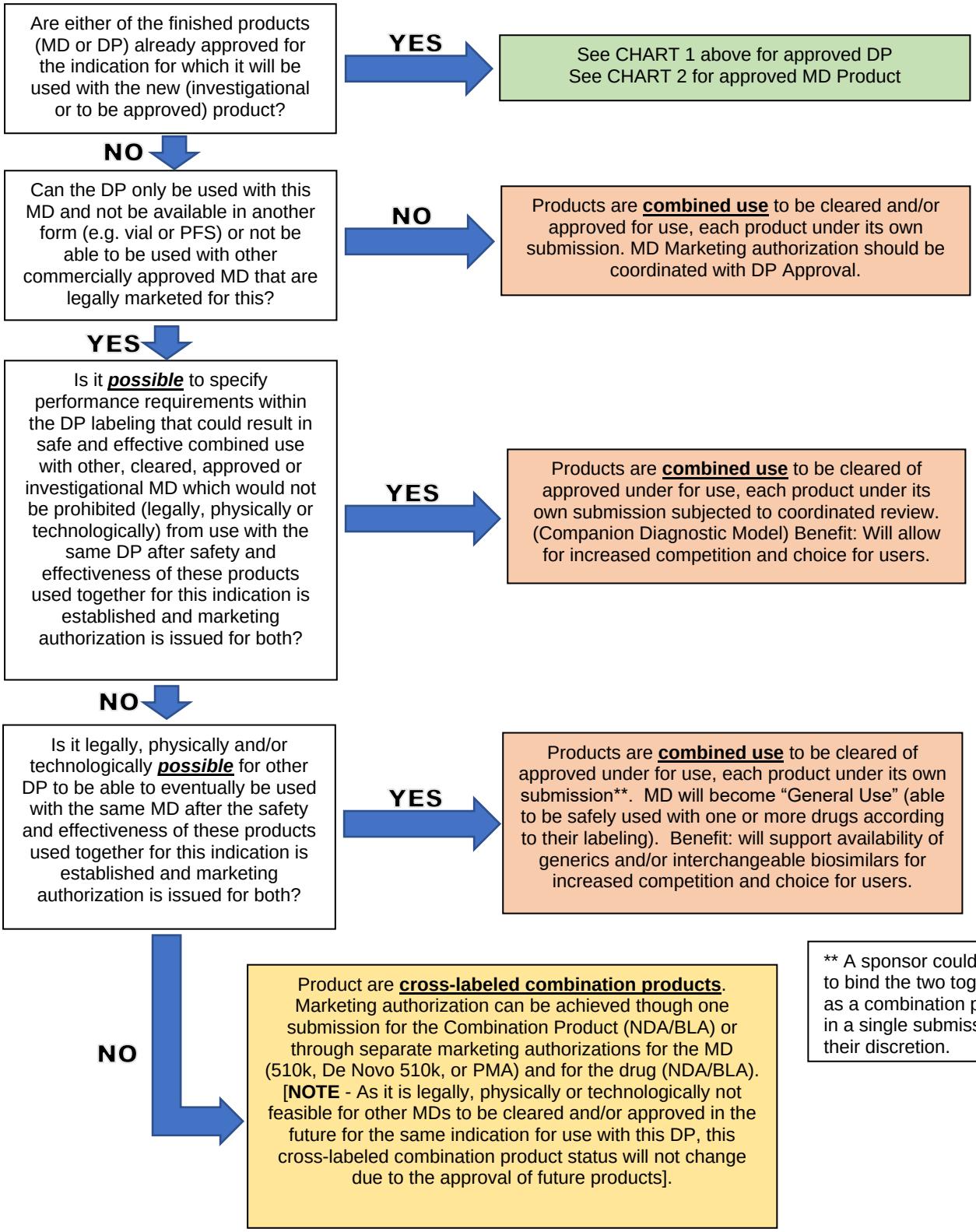
NO to both → New DP is a **combined use product** to be tested, studied and approved under an NDA/BLA or supplement for use with MD specified by brand (one-way labeled), specification (characteristics) or by MD labeled for use with this DP (according to sponsor preference or specifics of the use case)*.

YES to either

Both Products are now unapproved (investigational) Restart at the third box in **CHART 3** for TWO Investigational Products Chart

* If the decision is made to change the MD label to be indicated specifically for this drug. A separate device submission may be needed after the DP Approval. Then this would follow Chart 1 starting at box 4.

CHART 3
TWO Investigational Products Decision Tree



Appendix: Additional Background

Previous FDA work on this topic with industry includes the FDA/DIA Cross Labeling Workshop held on 10 May 2005[21], the Devices Referencing Drugs (DRD) Workshop held on 16 Nov 2017[22], proposed updates to the Product Jurisdiction Rule[23] published in May 2018 (83 FR 22428[24]), and the draft guidance *Principles of Premarket Pathways for Combination Products*[25] published in Feb 2019.

Industry has commented on this topic throughout the dockets for the actions referenced above, including:

- PhRMA[26] and Combination Product Coalition (CPC)[27] comments to the DRD docket[28].
- PhRMA[29] and CPC[30] comments to the docket for the proposed changes to the Product Jurisdiction Rule.
  - PhRMA: Reference third item within the comments.
  - CPC: Reference Section I and II, particularly the last paragraph of Section I.
- PhRMA[31] and CPC[32] comments to the *Premarket Pathways* draft guidance
  - PhRMA: Reference Comments 1 & 2 (relating to Sections A and B of the main body of comments).
  - CPC: Reference Comment 1 in the body and related comments within Appendix A.

Additionally, we note that the Request for Designation (RFD) process is available to provide formal designation of combination products. While RFD decisions are made public[33], the pre-RFD process is necessarily opaque and does not afford the rest of the industry the opportunity to incorporate those decisions.

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[21] http://wayback.archive-it.org/7993/20180125074743/https://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm116623.htm
[22] https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/devices-referencing-drugs-public-hearing-request-comments
[23] 21 C.F.R. §3
[24] https://www.govinfo.gov/content/pkg/FR-2018-05-15/pdf/2018-10321.pdf
[25] https://www.fda.gov/media/119958/download
[26] https://www.regulations.gov/contentStreamer?documentId=FDA-2017-N-5319-0014&attachmentNumber=1&contentType=pdf
[27] https://www.regulations.gov/contentStreamer?documentId=FDA-2017-N-5319-0002&attachmentNumber=1&contentType=pdf
[28] FDA-2017-N-5319
[29] https://www.regulations.gov/contentStreamer?documentId=FDA-2004-N-0191-0015&attachmentNumber=1&contentType=pdf
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[31] https://www.regulations.gov/contentStreamer?documentId=FDA-2019-D-0078-0009&attachmentNumber=1&contentType=pdf
[32] https://www.regulations.gov/contentStreamer?documentId=FDA-2019-D-0078-0005&attachmentNumber=1&contentType=pdf
[33] https://www.fda.gov/combination-products/classification-and-jurisdictional-information/rfd-jurisdictional-decisions

Finally, limited guidance is available for some "combined use products," such as the final guidance *Evaluation of Devices Used with Regenerative Medicine Advanced Therapies*[34], though that is only applicable to certain types of biologic products regulated by CBER.

[34] https://www.fda.gov/media/120266/download