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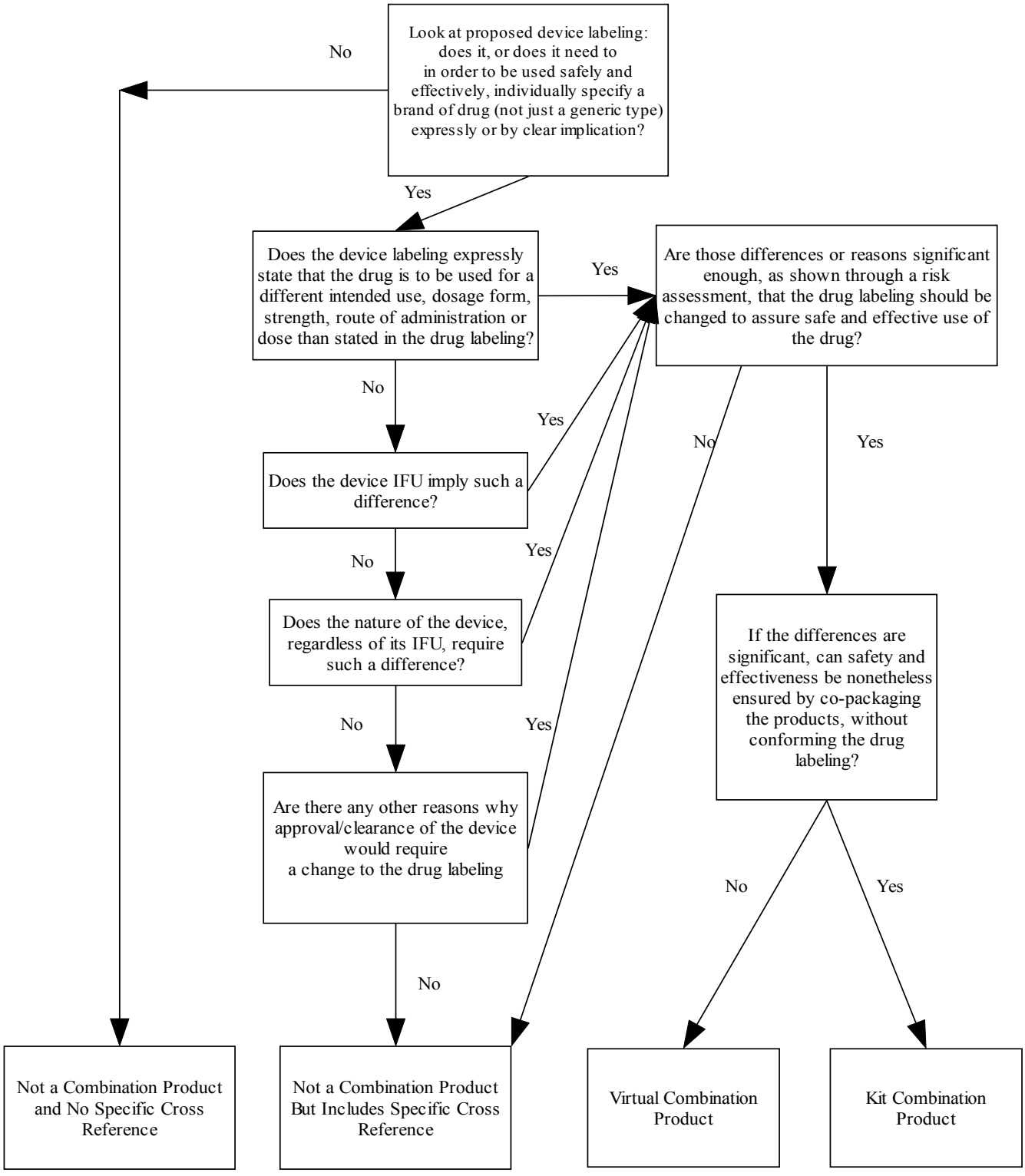
Regulatory Algorithm for Combination Product Cross Labeling Issue

For starters, let's discuss what products do and do not qualify as combination products. In this regard, we are only focused on subsection 3 of the definition in 21 C.F.R. § 3.2(e), which provides that:

> A drug, device, or biological product packaged separately and 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.

Let's take the case of a new device being submitted for use with an already approved drug.

Flow Chart for Determining Whether Drug and Device Represent Virtual Combination Products



Regulatory Consequences of the Combination Product Determination

Category (taken from pervious flow chart)	Not a Combo Product and No Specific Cross Reference	Not a Combo Product But Includes Specific Reference	Virtual Combo Product
Is an agreement between the parties assuring coordination required to approve the device?	**No**	**Maybe**. If a specific reference is made by brand, an agreement may or may not be necessary, depending on a risk assessment The risk assessment would be prepared by the firm seeking the second approval (company B), without the cooperation of the other company (company A). This risk assessment would consider and address such issues as: (1) The likelihood that product A will be changed in the future. (2) The consequences of possible changes to product A. Here we would be concerned with any special consequences unique to the combination, as opposed to consequences that would occur regardless of whether product A is used alone or with product B. (3) The effectiveness of company B's ability to monitor product A for such changes. (4) The ability of company B to effectively label the combined use without the need to relabel product A (which establishes that combination product status is unnecessary).	**Yes**, an agreement between the two companies is required to assure that product and labeling changes are coordinated, including the initial relabeling of the drug to make conforming changes

		(5) Any other issues that bear on the ability of company B to assure the safety and effectiveness of the combined product without the cooperation of company B. This risk assessment would be provided to FDA in the submission seeking clearance or approval for product B. For example, it could be a section of a 510(k) or PMA.	
Is a right of reference to the drug file required to approve the device?	No	Maybe	Yes, because the labeling of the approved drug will need to be changed, so the issues go beyond the mere safety and effectiveness of the device alone.
Claim support	Must be able to support all claims in labeling, including any claim that the device enhances the safety or effectiveness of the drug. Being able to support a claim means having the data in hand, or having permission to reference data owned by another.	Same	Same
Should the approval be conditioned on anything?	No	Maybe	Yes, on conforming changes to the drug labeling
What authorities can FDA use after approval?	Drug for the drug and device for the device	Same	Same