Number of Marketing Applications for a Combination Product

Purpose. The Office of Combination Products (OCP) is working to clarify the number of marketing applications necessary for a combination product, particularly the issue of whether a single or multiple marketing applications should be submitted for a combination product. OCP is very interested in receiving suggestions and comments from a wide variety of stakeholders on how this issue should be clarified. In order to stimulate stakeholder input, this concept paper describes possible approaches to address this issue. This document is being made available for comment purposes only. It does not represent FDA policy or guidance, and it does not create any obligation on FDA or any other person or entity.

OCP welcomes comments from interested stakeholders on (1) the general directions outlined in this paper or other directions stakeholders may wish to suggest, (2) the mechanism(s) needed for implementation of any policy regarding this topic (e.g., rulemaking, guidance), and (3) any other issue(s) that stakeholders believe should be addressed in future policies on this topic.

In the interim, FDA encourages applicants who are uncertain as to whether a single or multiple marketing applications should be submitted for a particular combination product to contact OCP.

General Principles. A combination product is assigned to an Agency center that will have primary jurisdiction for its premarket review and regulation. The assignment of a "lead center" is based upon a determination of the "primary mode of action" (PMOA) of the combination product, but a combination product's PMOA does not automatically determine the type of marketing application that will be used for the product's approval, clearance, or licensure. Depending upon the type of combination product, approval, clearance or licensure could be obtained through submission of a single marketing application, or through separate marketing applications for the individual constituent parts of the combination product.

As further explained below, for most combination products, a single marketing application is sufficient for the combination product's approval, clearance or licensure. In some cases, however, a sponsor may choose to submit two marketing applications for a combination product when one application would suffice. For example, a sponsor may choose to submit two applications in order to receive some benefit that accrues only from marketing authorization under a particular type of application (e.g., new drug product exclusivity, orphan drug benefits, or proprietary data protection when two firms are involved).

In other cases, FDA may determine that two marketing applications are necessary. For example, when one of the individual constituent parts of a combination product is already approved for another use, and where the labeling of the already approved product will need to be changed to reflect its new intended use in the combination product, FDA may determine that two applications are necessary if the labeling of the already approved product

is subject to legal requirements different from those that will apply to the combination product.

When might one marketing application be appropriate?

For most combination products, a single marketing application should be sufficient to ensure product safety and effectiveness as well as to ensure consistent and appropriate postmarket regulation. Under such an approach, this would be accomplished by applying, as appropriate, the regulations, standards, and mechanisms that are already available and applicable under the marketing application being used, along with those that accrue directly to the constituent parts. Review of the marketing application would address the combination product as a whole and its constituent parts.

In certain circumstances, it could be that a single marketing application is the only feasible option, such as:

- For combination products that are chemically, physically, or otherwise combined into one single entity (21 CFR 3.2(e)(1)). Drugs and devices are generally approved or cleared only as finished products, not as components for further manufacture.[1]
- For most co-packaged combination products (21 CFR 3.2(e)(2)), particularly those with constituent parts that could not be provided separately. Examples might include those co-packaged combination products where one of the components is not sufficiently finished to support a separate approval/clearance, or where the indication exists only in the co-packaged configuration.
- For combination products for which separate applications would create a regulatory inconsistency.

OCP is interested particularly in stakeholder perspectives on these examples and whether there are other examples where one application would be the only possible feasible option.

When might two marketing applications be necessary for a combination product?

Generally, the *necessity (from a regulatory perspective)* for two marketing applications has been infrequent historically.

However, there are some circumstances in which two marketing applications could be necessary for a combination product in order to ensure safety or effectiveness or consistent or appropriate postmarket regulation because regulatory provisions may be necessary that are

[1] Unlike the Food, Drug, and Cosmetic Act, the Public Health Service Act provides for the licensing of intermediate products used in the manufacture of specifically identified biological products. Consequently, a biologic-device or drug-biologic combination product with two components that are physically or chemically combined during their manufacture, could have a second marketing application (i.e., a "BLA for further manufacture") for the biological component if the combination product as a whole is being regulated under the device or drug provisions of the Act. In some cases, FDA may determine such an approach is necessary in order to ensure appropriate premarket review and regulation of the biological product component.

not available under the particular marketing application being submitted for the product. In such cases, one proposal might be that an additional marketing application is necessary in order to apply these provisions. Below are some examples intended to illustrate when two applications might be necessary:

- For combination products where the constituents are separate and complex products (e.g., drugs and implantable delivery pumps, device in combination with a new molecular entity).
- For constituent parts with uses beyond the combination product; e.g., a single dose drug and a reusable delivery device that is used for delivery of other drugs.
- When a "BLA for Further Manufacture" (see footnote 1) is appropriate to ensure the identity, safety, purity and potency of certain biological products (e.g., cell and gene therapy, therapeutic proteins, monoclonal antibodies, blood products) when the combination product as a whole is being regulated under the device or drug provisions.
- To effect labeling revisions for a constituent part that is already approved for uses that do not include the proposed combination product indication. For example, when a previously PMA-approved drug delivery device is later approved to deliver an additional drug, the labeling of both the additional drug and the device are typically changed in order to reflect their use in combination.
- To apply mechanisms necessary to ensure appropriate regulation, or unique regulatory requirements that are not available under a single marketing application, e.g., gene therapy products.
- To maintain regulatory consistency. For example, for a device co-packaged with a drug covered by new drug product exclusivity, a separate NDA or ANDA may be necessary for the drug constituent part.

OCP is interested particularly in stakeholder perspectives on these examples and whether there are other examples where two applications would be the preferred regulatory approach.

When might FDA accept two marketing applications when a single marketing application would be sufficient?

Just as certain regulatory mechanisms are available only under a specific type of marketing application, certain benefits, such as new drug product exclusivity or orphan drug benefits, are associated only with specific types of marketing applications. Sponsors may wish to derive specific benefits that accrue under different statutory/regulatory provisions and may sometimes wish to submit two marketing applications when one would otherwise suffice in order to accomplish marketing authorization. In addition, there have been situations historically in which separate companies are involved in the manufacture of finished products used in combination, such as for a drug/biological product and its delivery system, or for a drug/biological product used with a diagnostic device. In these situations, the sponsors have often preferred two applications.

OCP is interested in stakeholder perspectives on appropriate FDA responses when sponsors desire to have multiple applications, when one would generally suffice for product authorization purposes.

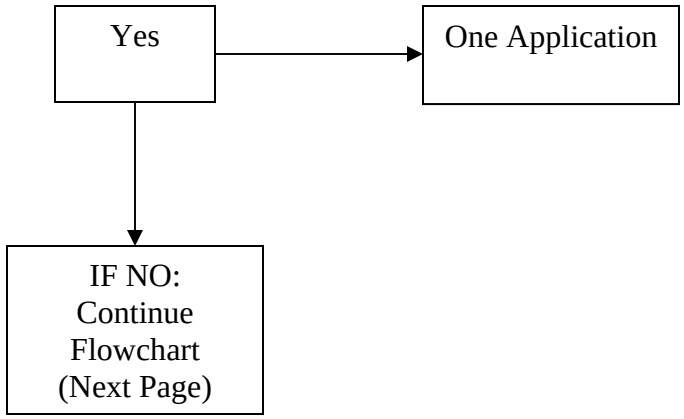
Some possible approaches may be to accept two applications when (1) the constituent parts of the combination product are provided in finished form and are separable from the other constituent parts of the combination product and (2) multiple applications would support independent regulatory approval for use in the combination product and would not create regulatory inconsistency.

Flow Chart:

A flow chart follows that displays a hypothetical flow diagram for a process for determining whether one or multiple marketing applications would be necessary. OCP is especially interested in: (a) stakeholder thoughts on this diagram and (b) whether such a vehicle is helpful to stakeholders.

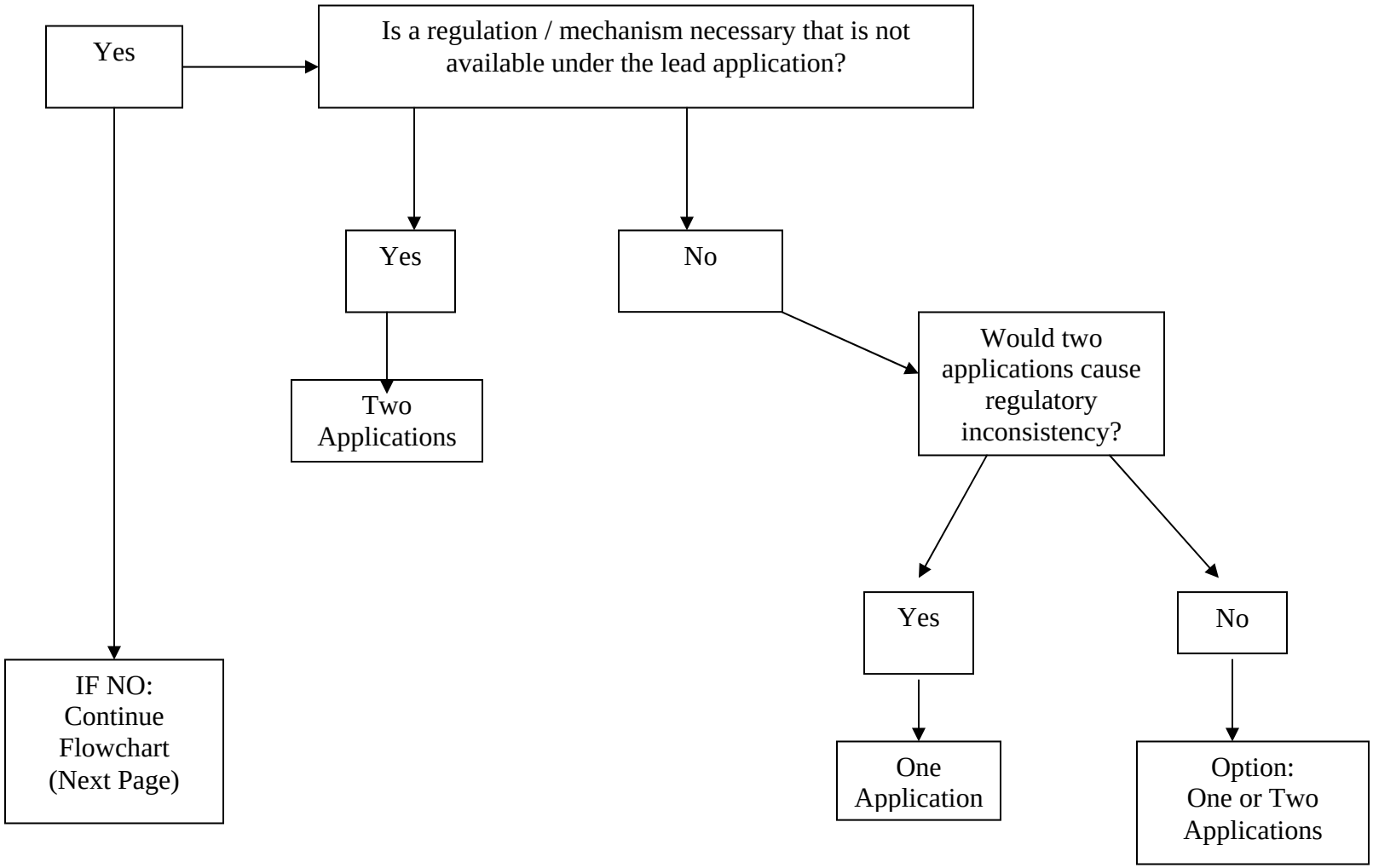
Flowchart: Possible Approaches to Determining the Number of Marketing Applications for a Combination Product[2]

Is the combination product chemically, physically, or otherwise combined and provided as a single entity as defined under 21 CFR 3.2(e)(1)?



[2] *For combination products with a biological product constituent part where the combination product as a whole is being regulated under the device or drug provisions of the Act, a separate BLA for further manufacture may be necessary or desirable.*

Are the constituent parts of the combination product provided separately as defined under 21 CFR 3.2(e)(3) or (4)?



Is the combination product provided as a co-package as defined under 21 CFR 3.2(e)(2)?