



Structuring Combination Product Marketing Applications

By Michael Gross, PhD, RAC

This article, the third in a series on FDA regulation of combination products, considers the structuring of combination product applications and its effect on downstream regulatory issues. It, along with two previous articles that discuss the problems in regulating combination products¹ and combination product terminology,² serves as a foundation for the remainder of the articles in this series.

Application structure can be a complex issue for a combination product. The term refers to the number of applications, the relationship between applications when more than one is involved and the content of these applications. It might seem that a single marketing application would suffice for a combination product but this is not always the case. Under certain circumstances it may not even be necessary to file any new application. Under other circumstances, more than one application may be needed or desirable.

Current Regulatory Framework

Drugs and Biologics

Predicate FDA regulations that address marketing applications for drugs or biological products describe the format and content of a New Drug Application (NDA)³ and Biologic License Application (BLA).⁴ The format and content are further specified in FDA Form 356h. These regulations also pertain to drug and/or biologic constituent parts of a combination product application. It is not clear if combination products have been approved through an Amended New Drug Application (ANDA), but 505(b)(2) approvals have been used for combination products with a drug primary mode of action.

Medical Devices

The marketing application for a combination product containing a medical device constituent part will follow, in part, regulations describing the format and content of Premarket Approval (PMA) applications⁵ or Premarket Notification Applications (510(k)).⁶

Combination Products

How these predicate rules are to be applied in formulating the application structure for a combination product is not specified in FDA regulatory

documents. FDA has published a concept paper on the number of marketing applications that may be filed for a combination product.⁷ The document, issued to stimulate stakeholder input, considers only the number of applications that may be needed to apply for marketing authorization for a combination product.

FDA recognizes that combination product approval, clearance or licensure may be obtained through submission of a single marketing application or through separate marketing applications for the constituent parts. The concept paper suggests that for most combination products, a single marketing application should be sufficient but an applicant may choose to submit more than one application. The concept paper also suggests that for single-entity combination products and kits containing constituent parts that cannot be provided separately, filing a single application may be appropriate. However, when the constituent parts of a combination product are separate and complex, or when constituent parts have labeled uses beyond that of the combination product, filing multiple applications may be necessary. Nonetheless, when assessing single or multiple applications, FDA considers existing regulatory frameworks for both the constituent part with the primary mode of action and the constituent part with the secondary mode of action.

In the concept paper, FDA allows there may be circumstances where a sponsor chooses to submit more than one application to gain access to a particular regulatory benefit that may be associated with a particular type of marketing application. Multiple applications might also be filed to protect the confidentiality of certain information that may be required by FDA. Or, the agency may require applications to be structured in a particular way. For example, when one of the constituent parts of a combination product is already approved for another use and its labeling needs to change to reflect its new intended use in a combination product, FDA may determine that two applications are needed. Further, FDA may impose a particular application structure to maintain regulatory consistency.

FDA's recently published draft guidance on drug delivery injectors⁸ provides additional insight into agency thinking on combination product application structure. The draft guidance recommends filing a single marketing application for a

drug or biologic prefilled injector, a single-entity combination product. However, if the injector is a general use medical device and the injection system is assembled by the user from a syringe or cartridge and the injector, then two applications may be involved, one for the drug product and one for the injector. The draft guidance also provides some insight into FDA's thinking on the content of NDA or BLA applications that incorporate a device constituent part. It mentions that when following the ICH Common Technical Document (CTD) format, some applications have included injector information in subsections of Module 3. Presumably, injector information could be incorporated as container closure information and/or extended to specifications, manufacturing, stability, suitability, pharmaceutical development, process validation and, possibly, other Module 3 drug product sections.

Application Structure and Combination Product Type

In simple cases, the application structure for cross-labeled and single-entity combination products is straightforward. Cross-labeled combination products involve separate presentations of different medical products, which are related through labeling. Here it seems likely that separate marketing applications would be filed. It is not clear if and how these applications would need to be connected. At a minimum, the constituent parts are connected through their labeling and stated intended uses, but the current FDA regulatory framework for combination products does not describe how the content of the marketing applications might serve to link applications. It would seem that to ensure the safety, effectiveness and quality of a cross-labeled combination product, linkage between the constituent applications should be established in some way. Single-entity combination products most likely involve single marketing applications, but there may be circumstances where this may not be ideal and the filing of multiple applications may be considered. Examples of single applications for single-entity combination products include several NDAs and BLAs for prefilled drug delivery systems and PMAs for drug-eluting stents.

Kits are more complicated when it comes to application structure. Two possibilities exist for kits: a new single application and no (new) application. FDA's concept paper suggests that for a kit, a new marketing application is needed when the constituent parts cannot be provided separately. When certain convenience kits that are regulated by the Center for Devices and Radiological Health (CDRH) are comprised of previously approved or cleared constituent parts that are used according to their intended use, CDRH may exercise regulatory discretion and not require the filing of a new application for the resulting kit combination product.⁹ If kit manufacturing can significantly alter the safety



or effectiveness of any of the constituent parts, an application may be required.¹⁰ Kit combination products that are not exempted from CDRH application requirements also require a new marketing application. When a new product is formed through co-packaging, a new application is obviously required. For example, fibrin sealants¹¹ are typically composed of biological products that form a fibrin clot co-packaged with an applicator. These biologic + biologic + device combination products are typically filed in a BLA.

If a drug delivery device is co-packaged with an approved drug or biologic, an application will be needed to describe this presentation. If a drug delivery device is added to an existing, approved drug or biological product through co-packaging, the "Dosage and Administration" and "How Supplied" sections of the approved package insert need to change through the filing of a labeling supplement (sNDA or sBLA).

Downstream Issues

The management of downstream issues is influenced by how applications are structured. Reporting manufacturing or design changes to a constituent part of a cross-labeled combination product supported by two applications should be straightforward. A change to one constituent part would be filed to the application describing that constituent part according to the reporting rules associated with that application. However, this may be less straightforward if there is some linkage in the manufacturing descriptions or specifications contained in the applications for the constituent parts.

The situation for a single-entity combination product filed in a single application is more complex. The rules when the constituent part with the primary mode of action undergoes change may be different from those when the constituent part associated with the secondary mode of action undergoes change. When change occurs in a kit combination product, reporting the change depends upon the application structure. If there is no application supporting the marketing of the kit, there is no place to report a change in kit manufacture. A change in the manufacture of one of the constituent parts of a kit combination product would be reported to the underlying applications according to the rules on reporting

changes to such applications. The reporting of manufacturing changes will be further discussed in a future article in this series.

It also may be more straightforward to submit safety reports for a combination product when multiple applications are involved for a single application. Anticipated FDA guidance on safety reporting for combination products may provide clarity. Similarly, structuring of quality systems for combination products may be simpler when one constituent part is described in one application and the other constituent part is described in another application. Clarification of this particular downstream issue also awaits proposed FDA regulation.



Other Considerations

When a medical device manufacturer wishes to gain clearance or approval to establish a platform device technology that may be combined with drugs or biological products, it may wish to file a separate application for the device. Information describing the device could be filed in a Device Master File (MAF) but there may be marketing advantages in obtaining a standalone marketing approval or clearance.

To gain access to special regulatory benefits, it may be necessary to file more than one application for a combination product. For example, it may be possible to gain exclusivity under the *Hatch-Waxman Act* or orphan drug status for a specific use of the drug constituent of a combination product with a device primary mode of action if the application structure allows for filing both a PMA and an NDA. Such exclusivity might not be available if only a PMA was filed.

When filing multiple applications for a combination product, user fees should be considered. Should an applicant choose to file multiple applications, FDA will collect multiple user fees.

Summary and Recommendations

Currently there are no FDA regulations or guidance on how to structure applications for combination products. Management of a particular combination product downstream issue will depend, in part, upon combination product type and application structure. Structuring applications for single-entity and cross-labeled combination products may be relatively straightforward, while structuring applications for kits may be more complex.

Planning is an important step in the submission of an application to any regulatory body. How an applicant plans to structure a marketing application for a combination product should be determined, in part, by considering existing rules describing the format and content of applications related to the individual constituent parts. Applicants should consider identical, similar or analogous regulatory precedents identified through regulatory intelligence activities. Also to be considered is the impact of a particular



submission strategy and application structure on how certain postmarketing requirements, originally intended to apply to a particular type of medical product, may be applied to a particular combination product. Before submission, application structure for a combination product should be always be discussed with appropriate reviewing staff of the FDA center with primary jurisdiction.

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