



Reporting Manufacturing and Design Changes to Combination Product Marketing Applications

By Michael Gross, PhD, RAC

This article, the sixth and final in a series on US Food and Drug Administration (FDA) regulation of combination products, covers reporting of postapproval (and postclearance) manufacturing and design changes to marketing applications (and notifications). Reporting change is the most complex of the combination product downstream issues.¹ It involves determining when a change must be reported, when it can be implemented and the content of reports describing the change to be submitted to the agency. Drugs, biologics and medical devices have distinct rules about what constitutes a minor, moderate or major change, and different kinds of approval are required for manufacturers to effect these changes. How to apply these rules when different medical product types are combined is a complex problem. That a combination product can be formed in at least three ways and the resultant combination product types may be filed in single or multiple marketing applications further complicate the matter. The large number of possibilities makes it difficult to establish specific rules or algorithms to aid in decision making for reporting. Therefore, this article discusses only general approaches to reporting manufacturing and design changes to combination product marketing applications.

Current Regulatory Framework

The rules for reporting changes to the manufacturing process of either a drug substance or a drug product, beyond variations established in an approved New Drug Application (NDA), are described in 21 CFR 314.70 and in Section 506A of the *Food, Drug, and Cosmetic Act*. Three levels (i.e., major, moderate, minor) of change are based upon the potential of the change to have an adverse effect on the drug product's identity, strength, quality, purity or potency as related to its safety or effectiveness. The reporting category for a particular change, as defined in FDA guidance, may be reduced if predefined comparability criteria are met in a successfully exercised comparability protocol.² This protocol may either be included in the original marketing application or submitted as a postapproval supplement (sNDA).

In general, major changes after NDA approval are reported in Prior Approval Supplements (PAS), which require agency approval before a product manufactured according to the altered process is commercially distributed. Depending upon specifics, moderate changes may be implemented either immediately (Changes Being Effected, CBE-0) or 30 days after FDA is notified of the intent to make a change (Changes Being Effected in 30 days, CBE-30), as long as no objection is raised following preliminary review. A limited number of specified minor changes can be reported in an annual report (AR). The majority of manufacturing changes to a combination product that has been approved under an NDA or Biologic License Application (BLA) are likely to be submitted in supplements (i.e., PAS, CBE-30, CBE-0) since only a few types of minor manufacturing changes may be submitted in an AR.

The rules for reporting changes to a BLA are described in 21 CFR 601.12. As with drugs, reporting categories for biologics are based on the potential for a particular change to adversely affect the product's identity, strength, quality, purity or potency as related to safety or effectiveness. While the details as to what constitutes a major, moderate or minor change are somewhat different for biologics, the rules generally follow the same paradigm for reporting changes to NDAs.

The rules for reporting changes to medical device Premarket Approval Applications (PMAs) are described in 21 CFR 814. These rules are more complex than those that apply to drugs and biologics. If the change negatively affects a device's safety or effectiveness, a new PMA approval is required before commercial distribution. Major design or performance changes are filed in traditional PMAs. Should a change require clinical data to provide assurance of safety and effectiveness, the change is filed in a Panel-Track Supplement. If a change enhances safety or effectiveness, a Special PMA Supplement—Changes Being Effected may be submitted. If FDA finds the submitted information to be inadequate, the submission may be converted to a 135-Day Supplement. A 180-Day Supplement may be filed for certain significant changes affecting safety or effectiveness. In general, for a change to be submitted as a 180-Day Supplement, clinical data in the original PMA

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must be representative of the modified device. Certain minor changes may be reviewed jointly by FDA and the sponsor through a Real-Time PMA Supplement, and other minor changes that do not affect product safety or effectiveness may be submitted in postapproval periodic reports required by the approval order.

Rules for reporting changes to a medical device cleared under a 510(k) notification are described in 21 CFR 807.81(a)(3)(i-ii). In general, changes in design, components or manufacture of a cleared medical device require filing a new 510(k) for the modified device if the change could significantly affect the device's safety and performance. A Center for Devices and Radiological Health (CDRH) guidance³ describes when and how the agency should be notified of such changes and the circumstances under which alternative approaches to the filing of a new 510(k) may be taken. For example, the guidance describes circumstances where Changes Being Effected or Special 510(k) filings can fulfill premarket notification requirements to market a modified medical device that was previously cleared. The guidance also describes situations where simply documenting test-based decision making providing evidence that the manufacturer's quality system assures the modified device's safety and effectiveness can be utilized.

Currently, there is no regulation or general guidance on how to report manufacturing or design changes to a combination product marketing application. Neither is there any rule or general guidance on how predicate rules for reporting changes to marketing applications for drugs, biologics and medical devices should be applied to combination products composed of these constituent parts. Insight into FDA's thinking on reporting changes to combination product marketing applications may be gleaned from a companion document to a draft guidance on nonclinical and clinical studies of a specific combination product, a drug eluting coronary stent approved under a PMA.⁴ It suggests that in certain instances, a sponsor may not need to perform preclinical or clinical tests to demonstrate that a particular drug-coated coronary stent is the same as a previously tested stent. Retesting can be avoided if the sponsor certifies that the specified change in stent sterilization or manufacture, or the drug formulation or manufacturing components, produces a stent that is the same as that produced without the change. While the document is specific to drug-coated coronary stents, it may suggest that in the future, comparability protocols and/or sponsor certifications of "sameness" could be useful approaches in the approval process for combination product manufacturing and design changes.

Effect of Application Structure

The simplest cases for reporting change to combination product marketing applications involve

kits and cross-labeled combination products. For certain kits that combine separately cleared or approved medical product constituent parts and that do not require an additional application to support their marketing, an appropriate report to the application for the constituent part undergoing change should be sufficient to support continued marketing. Similarly, for cross-labeled combination products formed by combining, through mutually conforming labeling, separately approved or cleared medical products, changes in the combination product would be filed to the application for the constituent part undergoing change. The difficulty in reporting combination product changes arises in cases where a single marketing application is filed (i.e., for single-entity and certain kit combination products). In these cases, where no regulations or guidance on how to apply predicate rules exist, and/or in the absence of specific postapproval reporting requirements imposed by the center with primary jurisdiction for the combination product's regulation, it is unclear how manufacturing or design changes should be reported.

Discussion

In the absence of regulation, guidance or postapproval reporting requirements specified in official correspondence (e.g., an approval order), a pragmatic approach should be taken when reporting a change in a combination product's design or manufacture. Unless it can be shown that there is a low risk that a specific change in a device-containing combination product will affect safety or effectiveness, most design or manufacturing changes should be reported to the respective marketing application. For single-entity or kit combination products filed in a single marketing application, a manufacturing or design change should be filed to that application. For cross-labeled combination products or kits not supported by an additional marketing clearance or approval, manufacturing or design changes should be filed to the application for the finished medical product constituent part undergoing change. If a biologic product constituent part of a combination product is made by divided manufacture and a change is to be made in the manufacturing process described in one of the BLAs that describes part of a larger biologic manufacturing process (i.e., divided manufacture), the description of the manufacturing change would appropriately be filed to its respective BLA according to rules for reporting changes to BLAs.

When the change is to the constituent part with the primary mode of action, a pragmatic approach can also be taken. For a single entity drug-device combination product filed in a single application, a change to the drug constituent part should be reported according to the rules for reporting change to an NDA. A change to the manufacture of the biologic constituent



part of a biologic-device combination product change should be reported according to the rules for reporting changes to a BLA. However, when a change occurs in the device constituent part (i.e., the constituent part with the secondary mode of action) of single entity drug-device or biologic-device combination products filed in a single marketing application, which predicate rule to apply is not obvious. There are several possibilities. In the case of a drug-device combination product, the rules for reporting changes to an NDA can be followed. In the case of a biologic-drug combination product, the rules for reporting changes to a BLA can be followed. In other words, the marketing application type controls the approach to be taken to report change.

Alternatively, a change to the device constituent part of a drug-device combination product could presumably follow the rules for reporting changes to medical device applications (i.e., according to either 510(k) or PMA rules, depending upon the device classification). In this instance, the constituent part type controls the approach to reporting change. It is not clear under these circumstances whether reporting a change to a medical device constituent part should follow 510(k) rules or PMA rules. If constituent part type is to control the approach to be followed, the sponsor might consider whether the standalone equivalent of the device would be cleared through a 510(k) or approved through a PMA and report the change according to the applicable rules. The aforementioned guidance for changes to 510(k) applications states it does not apply to combination products. However, for a specific pen injector, FDA has agreed to allow the 510(k) decision tree contained in this guidance to be applied to postapproval changes to the pen.⁵ Still, in the absence of an established agreement with the agency, in attempting to apply the constituent part type controls approach to this example, it is not clear which medical device rule to apply. Following the marketing application type controls approach seems to be a more reasonable choice. Another alternative would be to follow drug or biologic rules to report changes in a medical device constituent part. However, depending upon the specific change to the device design or manufacturing process being reported, this may be difficult since the rules for reporting changes to different medical product types are specifically tailored to those medical product types. In the case of a manufacturing change to the drug constituent part of a single-entity biologic-drug combination product (i.e., a change in the constituent part with the secondary mode of action), the pragmatic approach would be to follow regulations for reporting changes to a BLA. And, following this approach in the case of a single-entity drug-biologic combination product, the rules for making changes to the drug constituent would be applied to the biologic constituent

undergoing change. A more reasonable approach would be to follow the predicate rule specific to the constituent part undergoing change. The most conservative approach would be to follow the most stringent reporting requirements.

Conclusion

Postapproval changes that might occur during a combination product's lifecycle should be prospectively identified during its development. Prior to the issuance of marketing approval(s) and/or clearance, the sponsor and the FDA center with primary jurisdiction for regulating a particular combination product should establish a documented agreement on how such changes should be reported to the marketing application(s). The agreement should specify the type of reports that would be filed (e.g., sNDAs, PMA Supplements, 510(k) notifications), regulatory requirements to be satisfied before changes could be implemented for market production (e.g., after approval or 30 days after notifying FDA), content of the reports (e.g., comparability protocol, clinical data) and the details of comparability protocols and acceptance criteria, should comparability approaches be utilized to justify changes. When establishing such agreements, besides assessing the potential impact of a particular change on the constituent part, the impact on the entire combination product should be considered.

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