



Postmarket Safety Reports for Combination Products

By Michael Gross, PhD, RAC

Introduction

This is the sixth in a series of articles on the regulation of combination products by the US Food and Drug Administration (FDA). Currently there are no rules or guidance on submitting safety reports for combination products. This article considers how existing regulations for drugs, biological products and medical devices may be applied to postmarket safety reporting and looks at FDA's recently published proposed rule on this subject. Before the proposed rule, the only published agency commentary on postmarket safety reporting for combination products was a 2005 concept paper¹ issued by the Office of Combination Products, which discussed options FDA was considering to address this "downstream issue."² The proposed rule on postmarketing safety reporting for combination products³ provides insight into FDA's current thinking on requirements for the submission of postmarket safety reports. Rather than establishing a new safety reporting mechanism specific to combination products, the agency has chosen to build upon existing regulations. This article considers approaches to postmarket safety reporting that many combination product manufacturers are currently following and how these practices may need to change when a final rule is published and becomes an enforceable requirement. This article is neither a commentary on the proposed rule nor does it present a complete analysis of the rule.

Current Regulatory Framework

The predicate rules for submitting postmarket safety reports for drugs, biologics and medical devices to FDA describe conditions under which safety reports must be filed, the type of report to be filed and the required timing for these reports. Application of these rules to a combination product depends upon the product's type and primary mode of action, the number of underlying applications that support its marketing, the constituent part to which the adverse event is attributed and the kind of adverse event being reported. The rules for postmarket safety reporting for different medical product types that should be considered when reporting a combination product adverse experience are described:

- for drugs, in 21CFR 310.305 and 314.80
- for biological products, in 21CFR 600.80 and 606.170
- for medical devices, in 21CFR 803
- for blood and blood products, in 21CFR 606.170

These regulations contain important similarities and differences. The similarities stem from the common objective of protecting public health. They require reporting of deaths or serious adverse events associated with medical product use and describe the circumstances under which expedited reports are required. The differences stem from unique safety issues associated with these medical product types. Ambiguity over how to apply these rules to a combination product can produce underreporting or inconsistent safety reporting, potentially compromising the agency's ability to make informed decisions and take action to assure the safety of a particular type or class of product.

In the absence of specific direction from FDA, most manufacturers file postmarket safety reports for combination products in accordance with the requirements associated with the product's marketing approval, licensing or clearance mechanism. Most single-entity and many kit combination products are filed in single marketing applications that cover all of the constituent parts. For reasons discussed in a previous article in this series,⁴ sometimes separate marketing applications are submitted for the different constituent parts. The filing of postmarket safety reports for cross-labeled combination products is relatively straightforward. Where multiple approvals or clearances exist, drug or biologic adverse events can be filed according to New Drug Application (NDA) or Biologic License Application (BLA) rules and device-related adverse events can be filed as medical device adverse event reports (MDRs).

In the case of a combination product that is approved, licensed or cleared under a single application, when regulations require the submission of a report of an adverse experience, attribution of the adverse event to a particular constituent part is important. If the adverse event can be attributed to the constituent part of a combination product with the primary mode of action, generally the adverse event can be reported according to the rules associated with

its marketing approval, licensure or clearance. What has not been clear until now is how, under these circumstances, an adverse event attributed to the constituent part with the secondary mode of action should be reported.

Proposed Rule

FDA's proposed rule suggests that a combination product submitted for marketing approval or clearance under a single application would be, at a minimum, subject to safety reporting requirements associated with that application. For a combination product approved or cleared under the device provisions of the *Food, Drug, and Cosmetic Act*, an adverse event would be submitted as an MDR, according to 21 CFR 803; an adverse event for a combination product approved under an NDA would be submitted as an Adverse Drug Event, according to 21 CFR 314.80 and 21 CFR 314.81; and an adverse event submitted for combination products licensed under a BLA would be submitted as an Adverse Drug Experience, according to 21 CFR 600.80 and 21 CFR 606.170.

The proposed rule also recommends that unique elements of the postmarket safety reporting regulations related to the constituent part with the secondary mode of action be retained in a reporting scheme based on the combination product's marketing approval or clearance mechanism. The proposed rule identifies five such supplemental requirements:

- 5-Day MDR Report, described in 21 CFR 803.53(a), which requires an MDR to be filed no later than five business days following the occurrence of an event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health
- 30-Day Device Malfunction Report, described in 21 CFR 803.20(b)(3)(ii), which must be filed no later than 30 days after receipt of a report of the malfunction of a device; this requirement applies only to certain permanently implantable, life-supporting or life-sustaining Class II and Class III medical devices and Class I medical devices subject to quarterly summary reporting, if the malfunction of the device or a related device could recur and contribute to death or serious injury
- 15-Day Expedited Drug and Biological Product "Alert" Reports, described in 21 CFR 314.80(c)(1), 21 CFR 314.8(e), 21 CFR 600.80(c)(1) and 21 CFR 600.80(e), which requires filing of an adverse experience report no later than 15 days following notification of an adverse event for a drug or biological product that is both serious and unexpected; there is no MDR requirement for a 15-day report of an event that is



both serious and unexpected but reports of serious injury caused by the use of a medical device must be made within 30 days of the event

- 3-Day Field Alert Report, described in 21 CFR 314.81(b)(1), which is a provision unique to drugs and requires the filing of a field alert report for any bacteriological contamination, significant chemical, physical or other change or deterioration in a distributed drug product, or any failure of one or more distributed batches of the drug to meet the specification established for it in its marketing application, or any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; Field Alerts must be submitted by telephone or other rapid means of communication within three working days of receipt of the information and followed promptly by written follow-up to the responsible FDA district office
- Expedited Blood Fatality Report described in 21 CFR 606.170, unique to blood and blood components, requires notification of a confirmed blood collection- or transfusion-related death to be sent to the Center for Biologics Research and Review as soon as possible by telephone, facsimile, express mail or electronically transmitted mail with a follow-up written report submitted no more than seven days later

According to the proposed rule, when a single marketing application is filed for a combination product, depending on the nature of the reportable event, it may be necessary to submit additional safety information that would have been filed if the adverse event was attributed to the constituent part with the secondary mode of action as if it was not part of a combination product. This additional information would be necessary to ensure FDA receives all data needed to adequately assess risk and promote

and protect the public health. The proposed rule is not entirely clear about whether the additional information would be provided in a separate safety report of the type related to the constituent part to which the adverse event was attributed, or if it would be provided in the safety report associated with the type of approval, license or clearance under which the combination product is marketed. This information would be filed only if it was not otherwise reported to FDA, or if it would be required according to a shorter timeframe than the safety report related to the combination product's market authorization.

In cases where manufacturers have gained approval, licensure or clearance by filing multiple applications, they would need to comply with the requirements of each applicable regulation. Under these circumstances, however, it may not be necessary to file multiple safety reports if the adverse event can be attributed to a single constituent component of the combination product.

The proposed rule also suggests that when more than one applicant files for market approval, licensure or clearance of constituent parts of a single-entity combination product, (i.e., one applicant files for one constituent part while another files for another constituent part) each is subject to the applicable requirements for postmarket safety reporting for its constituent

part. Also, when a manufacturer of a constituent part of a combination product that is approved, licensed or cleared through multiple applications learns of an adverse event, a report must be made to FDA or the manufacturer of the other constituent part(s) within five days of receipt of this information. The proposed rule is not specific about what action should be taken if it is unclear which constituent part caused the adverse event.

The proposed rule does not address how manufacturers of convenience kits that have no clearance, approval or license beyond those of their constituent parts are to submit reports. Presumably, an adverse event related to one of the constituent parts of the kit would be reported according to the approval, license or clearance related to that part.

Depending upon their type, safety reports are submitted on a MedWatch form, a CIOMS form or Vaccine Adverse Event Reporting System form. For a combination product approved or cleared under a single marketing application, regardless of which constituent part is associated with the adverse event, the FDA center with primary jurisdiction for the regulation of the combination product (i.e., the lead center) would have primary responsibility for review.



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Discussion

Currently, most combination product manufacturers file postmarket safety reports according to the requirements related to the approval, license or clearance of their particular product. Until recently, it has not been clear to what extent manufacturers of single-entity combination products approved, licensed or cleared under a single marketing authorization must submit postmarket safety reports in accordance with requirements in addition to those associated with the marketing authorization. As a result, practices for reporting adverse events attributed to the constituent part with the secondary mode of action have been inconsistent. It seems clear now that for single-entity combination products, when an adverse event is attributed to the constituent part with the secondary mode of action, FDA wants manufacturers to provide additional information in accordance with requirements that go beyond those associated solely with the marketing authorization mechanism.

Conclusion

Other than clarifying FDA's expectations about postmarket safety reporting requirements for

single-entity combination products approved, licensed or cleared under a single application, the most significant impact of new regulations for combination product safety reports will be the need to restructure safety reporting systems within the healthcare products industry and the agency. Planning and implementing these changes will require significant resources and time, so manufacturers should begin preparations for compliance with the final rule.

References

1. Concept Paper: Postmarket Safety Reporting for Combination Products, Washington, DC: FDA Office of Combination Products; 2005.
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3. Proposed Rule: Postmarketing Safety Reporting for Combination Products (74 FR 50744). FDA; 22 September 2009.
4. Gross M. "Structuring Combination Product Marketing Applications." *Regulatory Focus*. 2009;14(9): 46-48.

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