Concepts for Comment Purposes Only – Not for Implementation

Postmarket Safety Reporting for Combination Products

Purpose. The Office of Combination Products (OCP) is working to clarify how postmarket adverse event reporting should be most appropriately handled for combination products. 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approaches to address adverse event reporting for combination products.[1] This document is being made available for comment purposes only.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 about how adverse events should be reported for their present combination products to contact OCP.

General principles. The postmarket safety reporting requirements for drugs, devices, and biological products share many similarities. For example, each requires reporting of deaths and serious adverse events, and for the submission of periodic or follow-up reports. FDA believes that for most combination products, appropriate postmarket safety reporting may be achieved by following the regulatory provisions associated with the type of marketing application used for its approval/clearance. However, the reporting requirements for drugs, devices, and biological products each have certain unique requirements based upon the products for which they were designed. For example, when a drug-device combination product is approved or cleared under the device provisions of the Federal Food, Drug, and Cosmetic Act (the Act), it is ordinarily subject to Medical Device Reporting (MDR) under 21 CFR Part 803. If the product was subject solely to Part 803, however, some of the reporting requirements that would have been applicable to the drug constituent part of the combination product had that drug been regulated under the drug provisions of the Act (and subject to postmarket reporting under 21 CFR 314.80) would not ordinarily apply. Conversely, had the same combination product been regulated under the drug provisions of the Act, some of the reporting requirements that would have been applicable to the device component of the combination product would not ordinarily apply.

To ensure consistent and appropriate postmarket regulation of combination products, and to ensure an appropriate ongoing assessment of the risks associated with a combination product, FDA is currently considering mechanisms by which the postmarket safety reporting requirements ordinarily associated with the marketing application used to approve or clear the combination product may be supplemented, as appropriate, to take into account the combination nature of the product.

[1] These comments are applicable only to mandatory reporting; they do not apply to voluntary reports.

One idea would be to develop a reporting scheme in which the same types of postmarket safety reports would be submitted for a combination product, regardless of the type of marketing application used for its approval or clearance.

The differences in the drug, device, and biological product postmarket safety reporting regulations that FDA currently believes are most significant to monitor and assess the risks associated with combination products are:

- **Device Malfunction Reporting** (21 CFR 803.3(r)(2)(ii), 21 CFR 803.20): In addition to the reporting of device malfunctions associated with a death or serious injury, the MDR regulation also requires reporting of device malfunctions where no death or serious injury occurred, but when such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur. Reporting for drugs and biological products does not include the analogous requirement; i.e., reporting of product failure that *could* result in a death or serious injury, but for which a patient event did not occur. In order to ensure consistent and appropriate postmarket regulation for some combination products with device constituent parts regulated under the drug or biological product provisions of the Act, device malfunction reporting may be necessary.

- **5-Day MDR Reporting** (21 CFR 803.10(c)(2)(i)): The MDR regulation requires reporting of (1) any reportable event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health, and (2) any MDR reportable event for which FDA has made a written request for the submission of a 5-day report. To ensure consistent and appropriate postmarket regulation, for some combination products regulated under the drug or biological product provisions of the Act, 5-day MDR reports may be necessary.

- **Drug and Biological Product "Alert" Reporting** (21 CFR 314.80(c)(1) and 600.80(c)(1)): For drugs and most biological products, postmarket safety reporting emphasizes adverse events that are both serious and unexpected. Although device safety reporting requires 30-day reports of any serious injury, the reports would not necessarily flag an event as both serious and unexpected, and they would be submitted at 30-days rather than the earlier "alert" reporting period of 15-days. In order to ensure consistent and appropriate postmarket regulation, for some combination products with drug or biological product constituents that are regulated under the device provisions of the Act, such "alert" reporting may be necessary.

- **Blood Related Deaths** (21 CFR 606.170)**:** The biological product regulations require reports to be submitted to CBER as soon as possible (e.g., by phone, fax or e-mail), with a 7-day written report of any blood related death. FDA believes that for some blood-containing combination products regulated under the device or drug provisions of the Act, such early notification of blood-related deaths may be necessary in order to ensure consistent and appropriate postmarket regulation.

OCP is very interested in whether stakeholders agree with these assessments and whether there are other provisions of adverse event reporting for biologics, devices, or drugs that stakeholders believe should be added to this list of significant differences.

What are some specific options that might be considered for adverse event reporting for combination products?

Combination Products Approved Under One Marketing Application. One option might be for a combination product approved or cleared under a single marketing application to be subject to the postmarket safety reporting requirements ordinarily applicable to products approved or cleared under that type of application and, in addition, be subject to the type of additional reporting identified above. For example, a drug-device combination product approved under NDA would, in this scheme, remain subject to the requirements specified in 21 CFR Part 314, as well as device malfunction and 5-Day MDR reporting as described above. A device-blood combination product approved under a PMA would, in this scheme, remain subject to Medical Device Reporting under 21 CFR Part 803, as well as 15-day "alert" reporting of serious and unexpected adverse events associated with the biologic constituent, and reporting of blood-related deaths, as appropriate.

Combination Products Approved Under Separate Marketing Applications. For some combination products, the constituent parts of the product are approved under separate marketing applications held by the same sponsor. In this situation, one option might be that when the most likely associated constituent part can be determined from the initial safety report (e.g., from a consumer, health care provider, or user facility), the sponsor would submit the safety report as ordinarily required for that constituent part. For example, if the event was most likely related to the device component of the product, an MDR would be submitted. If the initial safety report did not contain enough information to ascertain which constituent part may most likely be associated with the event, the sponsor would submit the type of safety report ordinarily received by the lead Center for that combination product. For example, if CDER was the lead Center for reviewing the combination product, the safety report would be submitted to the MedWatch mailing address for drug safety reports. If such an approach were to be adopted, OCP would be interested in knowing from stakeholders whether appropriate records with both application files should be maintained.

For combination products where the constituent parts are approved under separate marketing applications that are held by different sponsors, one option might be that each sponsor would comply with the safety reporting regulations ordinarily associated with the marketing application used to approve/clear its constituent part. OCP would be interested in stakeholder views on how to handle situations where a sponsor receives an adverse event report about a constituent part that was approved or cleared under the marketing application held by the other sponsor. Various possibilities include:

- If the initial safety report received by the sponsor clearly identified the constituent part thought to be associated with the event, and if that constituent was held by the other sponsor, the sponsor who received the report would send the report to the holder of the other marketing application for assessment of whether the report should be submitted to FDA.
- The sponsor who received the initial report would also maintain records of the initial report. Alternatively, the sponsor who initially received the report would submit the safety report to

FDA with a cover letter indicating the manufacturer and application number for the suspect constituent part.

- If the initial safety report did not contain enough information to identify which constituent part may have been associated with the event, then the sponsor who received the report would submit the report to FDA as it would for other reportable events concerning its product and provide a copy of the report to the application holder of the other constituent part.