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The More the Merrier: Knowing When, Why, and What to Tell FDA about Combination Product Postmarket Events

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Introduction

The US Food and Drug Administration (FDA) announced on December 20, 2016 that it is issuing final regulations governing postmarketing safety reporting for combination products.[1] The regulations become effective January 19, 2017. As discussed in more detail below, companies will have additional time—until July 19, 2018—to comply with some of the new reporting requirements provided for in the new regulations. The final regulation clarifies reporting requirements for:

— holders of applications covering the whole combination product; and

— holders of applications covering the individual constituents that make up a combination product.

Overall, the final regulation represents a significant transformation in how safety reporting must be handled for combination products. Companies involved in the commercialization of combination products and their individual parts will need to carefully assess this regulation to determine how it will impact their operations and what specific steps they will need to take to bring their reporting processes into compliance before the July 19, 2018 compliance deadline.

FDA's New Reporting Requirements

By statute, postmarket safety reporting obligations are tied to the type of marketing application covering the product. See 21 USC §§ 355(k) and 360l. Thus, because combination products, as defined in 21 CFR Part 3, include multiple types of constituent parts, FDA's new regulations are adapted to combination products approved or cleared in two different ways. Some combination products have multiple constituent parts approved under a single marketing application. For example, both the drug and device constituent parts of a combination product might be approved under a single new drug application (NDA). Other combination products have multiple constituent parts, each of which are approved or cleared under separate applications. For example, a biologic licensed under a biologics license application (BLA) might be labeled to be used in conjunction with a diagnostic device approved under a premarket approval application (PMA).

The main responsibilities for postmarket reporting requirements are defined by the application type that was the vehicle for allowing the product to be lawfully marketed. 21 CFR § 4.102(b). This is true whether the application covered only one constituent part of a combination product or covered the entire combination product with multiple constituent parts. Thus,

— If the application was approved under an NDA or an abbreviated new drug application (ANDA), the application holder must comply with the postmarket reporting requirements under 21 CFR part 314;

— If the application was approved under a BLA, the holder must comply with parts 600 and 606; and

— If the product received market authorization under a device application , the application[2] holder must comply with parts 803 and 806.

Single Marketing Application

The holder of a single application that covers multiple types of constituent parts (e.g., a drug and device component) has additional reporting responsibilities. 21 CFR § 4.102(c). Specifically, they must first meet all requirements for their product's application type. If the overall application is an NDA, the holder must meet all requirements of part 314; if a BLA, all requirements of parts 600 and 606; and if a device application, all requirements of parts 803 and 806. In addition, the application holder must meet certain requirements that account for the other constituent parts of the combination product as follows:

— For a non-device application that includes a device constituent part, the holder must submit: five-day reports, malfunction reports, and correction or removal reports, and/or maintain the records described in 21 CFR §806.20

— For a device application or BLA that includes a drug constituent part, the holder must submit: field alert reports and fifteen-day reports as described in 21 CFR § 314.80, but the fifteen-day reports must be submitted within 30 calendar days rather than 15 days if the drug constituent part is covered under a device application.

— For a device application or NDA that covers a biologic constituent part, the holder must submit: biological product deviation reports and fifteen-day reports as described in 21 CFR § 600.80, but the fifteen-day reports must be submitted within 30 calendar days rather than 15 days if the biologic constituent part is covered under a device application.

Beyond these event specific requirements, holders of an NDA, ANDA, or BLA that covers a device component must include summaries of five-day and malfunction reports in their periodic safety reports. 21 CFR § 4.102(d)(1). Holders of a device application that covers a drug or biologic do not have to make periodic reports unless specifically requested by the FDA. 21 CFR § 4.102(d)(2).

Multiple Constituent Parts, Each of Which are Covered Under Separate Applications

The holder of an application that covers only one of multiple constituent parts must also share certain information with the application holders for other constituent parts of a combination product. When a constituent part application holder receives a report of a death or serious injury under 21 CFR § 803.3, or an adverse experience under 21 CFR 314.80(a) or 21 CFR 600.80(a), the holder must provide the information within 5 calendar days to the holders of the applications for the other constituent parts of the combination product. 21 CFR § 4.103(a). The application holder that initially received the report must also maintain records of the information provided, the date the information was received, the date the information was sent, and the names and addresses of the other application holders. 21 CFR § 4.103(b).

The regulation also addresses submission of postmarketing safety reports for a holder of an application that covers only one of multiple constituent parts. The holder of an application that covers only one constituent part only needs to make reports for that application type – thus, an NDA holder only makes drug reports, etc. 21 CFR § 4.104(a). The holder of an application that covers multiple types of constituent parts submits all reports necessary for each type

of constituent part, but submits all of the individual case study reports (i.e., 15-day reports, malfunction reports, serious injury or death reports, and 5-day reports) to the center with authority over the main application type. 21 CFR §4.104(b). For example, the holder of a BLA that covers a biologic and a device would submit both biologic and device reports, but would submit all individual case study reports to CBER.

Recordkeeping Requirements

Finally, the new regulations address postmarketing safety reporting recordkeeping requirements. Holders of an application for a constituent part must maintain records applicable to the type of application they hold. 21 CFR § 4.105(a)(1). In addition, they must maintain records for the longest required period of any constituent part in the overall combination product. 21 CFR § 4.105(a)(2). Holders of an application that covers multiple constituent parts must maintain records for the longest time period applicable to any constituent part in the product. 21 CFR § 4.105(b). Where there is a device constituent part, record retention periods will often be driven by the device constituent part which is required by the QSR to be "retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer" (21 CFR § 820.180(b)) because durable devices frequently have longer life cycle use periods than drugs or biologics.

Changes from Prior Requirements and Important Dates

The new regulations mark important changes in how firms must conduct postmarketing safety reporting. Before these new regulations were released, FDA expected adverse events to be submitted only in accordance with the application the combination product was approved under. But this approach sometimes led to reporting gaps that the new regulations are designed to fill. For instance, if a combination product was approved under a BLA but was used in conjunction with a diagnostic device approved under a PMA, the combination product mandated reporting only under BLA obligations pursuant to Parts 600 and 606. FDA did not require reporting for the device component under Parts 803 and 806 nor did it require the constituent parts manufacturers to share information about adverse events with one another. As such, in the past, the combination product application holder was not obligated to report a device malfunction at all unless it involved a death or serious injury. And, even where death or serious injury was involved, the combination product application holder needed to report the malfunction only according to the firm's BLA obligations—it was left to FDA's internal processes to refer the malfunction to FDA's device officials. Under the new regulations, however, a combination product application holder that becomes aware of a device malfunction in its product must also submit reports under device reporting obligations pursuant to Parts 803 and 806 and share that information with the device manufacturer.

Similarly, while holders of applications that cover a combination product's constituent parts have always needed to report under the constituent part's application type, constituent part manufacturers were not obligated to share information about adverse events with the manufacturers of the other constituent parts. Now, firms must do precisely that: report adverse events to holders of applications for all the other constituent parts of the product. See 21 CFR § 4.103(a).

The new regulations are effective on January 19, 2017. However, FDA has chosen to extend the compliance date regarding certain new reporting requirements to July 19, 2018 – 18 months following the regulations' effective date. The extended compliance date applies specifically to:

— Combination product applicants' new obligation to report under the regulations that govern its constituent parts pursuant to 21 CFR § 4.102(c) and (d).

— Combination product applicants' new obligation, pursuant to 21 CFR §4.105(b), to maintain records in accordance with the longest time period required for records applicable under 21 CFR § 4.102.

— Constituent parts applicants' new obligation to provide adverse event information within 5 calendar days to the holders of the applications for the other component parts of the product pursuant to 21 CFR § 4.103.

— Constituent parts applicants' new obligation, pursuant to 21 CFR § 4.105(a)(2), to maintain records in accordance with 21 CFR § 4.102(b).

Conclusion

Holders of approved applications for combination products and constituent parts have new reporting obligations under the new regulations. In some instances, the regulations simplify and formalize processes that firms have already undertaken. In other instances, however, the regulations impose additional requirements that may require affirmative steps to bring reporting processes into compliance before July 19, 2018. With these changes, longstanding gaps in the reporting obligations for combination products will be closed, thereby giving FDA more complete visibility to the performance of all constituent parts of combination products as well as better data with which to monitor the safety of the drugs, biologics, and devices approved for use with each other in the marketplace. In addition, by sharing information between manufacturers of combination products and their constituent parts, emerging safety signals or newly uncovered risks of product malfunctions are more likely to be detected. Put simply, the more the merrier (and safer, too).

If you have any questions about the final regulation and how it may affect your business or organization, please contact one of the authors of this alert or the Hogan Lovells attorney with whom you regularly work.

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1. https://www.gpo.gov/fdsys/pkg/FR-2016-12-20/pdf/2016-30485.pdf

2. FDA has defined "device application" to include a PMA, product development protocol (PDP), humanitarian device exemption (HDE), de novo classification request (request for classification under section 513(f)(2) of the FD&C Act), or premarket notification (510(k)) submission.

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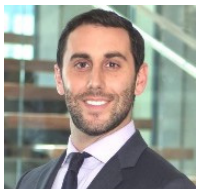

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