Compliance Policy for Combination Product Postmarketing Safety Reporting

Immediately in Effect Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

This guidance document is intended to assist Combination Product Applicants who are subject to the Combination Product Postmarketing Safety Reporting Final Rule (hereafter "combination product PMSR final rule," "final rule," or "rule"), issued on December 20, 2016 (81 FR 92603), and codified in 21 CFR Part 4, Subpart B. This guidance document discusses FDA's compliance policy for the rule. FDA does not intend to enforce certain requirements under the rule, specifically 21 CFR 4.102(c) and (d), 4.104(b)(1) and (b)(2), and 4.105(b), for a period of time as discussed further in section III below. FDA intends to delay enforcement of these provisions to ensure that Combination Product Applicants have sufficient time to update reporting and recordkeeping systems and procedures, including their information technology systems, to comply with these requirements, and in doing so, have sufficient time to consider the recommendations and technical specifications that FDA intends to provide through guidance to support compliance. For all other provisions of 21 CFR Part 4, Subpart B, FDA intends to enforce (or continue enforcing) the requirements per its usual policies as of the compliance date provided in the final rule.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

In the Federal Register of December 20, 2016 (81 FR 92603), FDA published a final rule for postmarketing safety reporting (PMSR) for combination products as defined at 21 CFR 3.2(e). The combination product PMSR final rule applies to combination products that are subject to premarket review by FDA. The entities subject to the final rule are "Combination Product Applicants," which are applicants that hold the only application for a combination product or all

the applications for the "constituent parts" (drug, device, or biological product) of a combination product, and "Constituent Part Applicants," which are applicants for a constituent part of a combination product the constituent parts of which are marketed under applications held by different applicants (see 21 CFR 4.100 and 4.101).

Under the final rule, Combination Product Applicants must comply with: application type-based PMSR requirements (PMSR requirements associated with the application type under which the combination product received marketing authorization) (see 21 CFR 4.102(a) and (b)), constituent part-based PMSR requirements (specified in the rule based on the types of constituent parts included in the combination product) (see 21 CFR 4.102(c) and (d)), and associated submission process and recordkeeping requirements (see 21 CFR 4.104(b) and 4.105(b)).

In the preamble to the final rule (81 FR at 92619), FDA stated that the compliance date for the application type-based PMSR requirements for Combination Product Applicants and Constituent Part Applicants under 21 CFR 4.102(a) and (b), and for the submission process and recordkeeping requirements for Constituent Part Applicants under 21 CFR 4.104(a) and 4.105(a)(1), respectively, was the same as the effective date for the final rule (January 19, 2017). These requirements are generally the same as for any other entity holding such an application for its product, and we expected all applicants subject to this rule to already be in compliance with these provisions as such provisions generally refer to existing regulations that such applicants have generally followed. With respect to the PMSR requirements of 21 CFR 4.102(c) and (d), 4.103, 4.104(b), and 4.105(a)(2) and (b), the final rule established a compliance date 18 months following the effective date of the rule (i.e., compliance date of July 19, 2018).

III. FDA's Compliance Policy for the Combination Product PMSR Final Rule

FDA does not intend to enforce the following provisions of the combination product PMSR final rule applicable to Combination Product Applicants prior to the dates provided in the bullets below: 21 CFR 4.102(c) and (d) (constituent part-based PMSR requirements), 4.104(b)(1) and (b)(2) (submission process for constituent part-based Individual Case Safety Reports (ICSRs)[1]), and 4.105(b) (recordkeeping requirements).

- July 31, 2020, for Combination Product Applicants using the FDA Adverse Event Reporting System (FAERS) and Electronic Medical Device Reporting System (eMDR) to report ICSRs.

- January 31, 2021, for Combination Product Applicants using the Vaccine Adverse Event Reporting System (VAERS) to report ICSRs.

[1] The term "Individual Case Safety Report" (ICSR) is used to describe a report of an event experienced by an individual user of a combination product, including adverse events and malfunctions. For purposes of the combination product PMSR final rule and this guidance, ICSRs encompass Fifteen-day reports (see 21 CFR 314.80, 600.80), Five-day reports (see 21 CFR 803.3, 803.53, 803.56), Malfunction reports (see 21 CFR 803.50, 803.56), and death or serious injury reports (21 CFR Part 803).

FDA intends to delay enforcement of the above provisions to ensure that Combination Product Applicants have sufficient time to update reporting and recordkeeping systems and procedures, including their information technology systems, to comply with these requirements. During the period of delayed enforcement, FDA intends to focus on educating Combination Product Applicants on the above provisions with which they may be less familiar, including providing guidance to help them comply with these provisions. The period of delayed enforcement will provide Combination Product Applicants with additional time to consider the recommendations and technical specifications that FDA intends to provide through the aforementioned guidance as they update their systems and procedures to comply with these provisions.

For all other provisions of 21 CFR Part 4, Subpart B, FDA intends to enforce the requirements per its usual policies[2] because FDA does not believe significant updates to systems and procedures are necessary to comply with these provisions.

[2] FDA's usual enforcement policies would apply in deciding whether to take enforcement action for violations in any given case, including the consideration of numerous factors such as whether the Agency's resources would be best spent on a particular case.