FDA Delays Enforcement of the Postmarketing Safety Reporting (PMSR) Final Rule for Combination Product Applicants

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The Food and Drug Administration issued a final rule setting forth postmarketing safety reporting (PMSR) requirements for combination products subject to premarket review by FDA on December 20, 2016.[1] For some of these requirements, FDA set a January 19, 2017 effective date as it was FDA's expectation that applicants already be in compliance with these PMSR requirements as they generally refer to existing regulations.[2] A later compliance date of July 19, 2018 was set for certain other PMSR reporting requirements.

To provide sufficient time for combination product and constituent part applicants to update reporting and recordkeeping systems to come into compliance with these requirements, FDA announced in March 2018 that it is delaying enforcement of certain provisions of the PMSR final rule.[3] Although portions of the rule have been in effect for some time and others will become effective July 19, 2018, the recent announcement is a good reason to not only describe the provisions subject to the continued delay of enforcement, but also to highlight the requirements currently in effect.

Background

Prior to the PMSR final rule, there were no postmarketing safety reporting requirements specifically for combination products. Instead, postmarketing safety reporting regulations applicable to the constituent parts of a combination product were applied. Each set of regulations for a constituent part (drugs, devices, and biological products) has certain unique reporting requirements and timeframes, which caused confusion and resulted in a lack of clarity on how to apply the requirements to combination products. The final rule provides clarification and a consistent approach to reporting and recordkeeping requirements related to certain postmarket events, including manufacturing events and events causing injury.

Requirements Under the PMSR Final Rule

The requirements of the final rule are applicable to combination product applicants and constituent part applicants (when the constituent part of a combination product is marketed under an application held by a different party).[4] The final rule clarifies that a sponsor must comply with the reporting requirements applicable to any product with the same type of marketing authorization, e.g., a combination product receiving marketing authorization under a device application must comply with the requirements for postmarketing safety reporting for medical devices.

The PMSR final rule also establishes additional reporting requirements specific to combination products. These additional reporting requirements include:[5]

1 The final rule is codified in 21 C.F.R. Part 4, Subpart B.

2 The initial effective date applied to the type-based PMSR requirements available at 21 C.F.R. 4.012(a) and (b), and the submission process and recordkeeping requirements under 21 C.F.R. 4.1904(a) and 4.105(a)(1) for constituent part applicants.

3 *See Compliance Policy for Combination Product Postmarketing Safety Reporting*, available here.

4 A constituent part is the device, drug, or biologic that is part of a combination product. 21 CFR § 4.2. The requirements do not apply to investigational combination products, combination products that have not received marketing authorization, or to persons other than combination product applicants and constituent part applicants. 21 C.F.R. § 4.100.

5 21 CFR § 4.102. These additional reporting requirements apply unless the applicant has already submitted a report that satisfies all of the applicable reporting requirements that is required to be submitted in the same manner or method and that meets all applicable deadlines.

- Five-day reporting requirements for combination products that contain a device constituent part after an applicant becomes aware either that a reportable event for the combination product requires remedial action to prevent an unreasonable risk of substantial harm to the public health or FDA has made a written request for the submission of a five-day report.

- Fifteen-day reporting requirements for combination products that contain a drug or biological product constituent part for "adverse experiences" that are both "serious" (any adverse experience that results in: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect) and "unexpected" (an adverse event that is not listed in the current labeling for the product).[6]

- Thirty-day malfunction reports are required for combination products that contain a device constituent part after the applicant receives or becomes aware of information that "reasonably suggests" that the product has malfunctioned and the product or a similar product would be likely to cause or contribute to a death or serious injury.

- Under the final rule, constituent part applicants are also required to share with other constituent part applicants for the combination product, within 5 calendar days from initial receipt, information on deaths or serious injuries or adverse experiences, if associated with the combination product.[7]

There are requirements under the final rule for submission of follow-up reports, field-alert reports, malfunction reports, biological product deviation reports, and correction or removal reports. The final rule also addresses the submission requirements, use of a single report to satisfy multiple reporting requirements and recordkeeping requirements.

Delayed Enforcement Dates

As noted above, the original compliance date for most requirements was in 2017, with a delayed phase-in for certain PMSR requirements set for July 19, 2018. FDA's March 2018 guidance document further delays FDA's enforcement of certain requirements under the final rule. The new deadlines are as follows:

- July 31, 2019, for combination product applicants using the FDA Adverse Event Reporting System (FAERS) and Electronic Medical Device Reporting System (eMDR) to report Individual Case Safety Reports (ICSR), which include fifteen-day reports, five-day reports, malfunction reports, and death or serious injury reports, as required by the PMSR final rule.

- January 31, 2020, for combination product applicants using the Vaccine Adverse Event Reporting System (VAERS) to report ICSRs.

During the period of delayed enforcement, FDA intends to focus on educating combination product applicants on the new requirements and how to comply with them. In addition, in accordance with the initial compliance dates, FDA will begin enforcing the requirements for constituent part applicants to share information on deaths or serious injuries or adverse experiences and the recordkeeping requirements associated with these events on July 19, 2018. All other requirements were subject to the initial 2017 compliance date.

AGG Observations

- Delay of the enforcement of these requirements suggests that FDA has received a large number of questions and comments on the guidance document.
- During the time of delayed enforcement, combination product sponsors should consider additional

6 Note, applicants for combination products marketed under a device application are required to submit such reports within 30 calendar days.
7 21 C.F.R. § 4.103.

recommendations and technical specifications for recordkeeping and reporting systems, and ensure that information technology systems are updated to allow compliance with recordkeeping and reporting requirements.

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