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Summary and Analysis

Final Rule Post-marketing Safety Reporting for Combination Products

For information purposes, the following contains a brief summary and interpretation of FDA's Final Rule on combination product post-marketing safety reporting. For regulatory purposes, refer to 81 FR 92603-92626 for the regulation and preamble.

FDA has published a long anticipated Final Rule (Rule) on post-marketing safety reporting (PMSR) for combination products [and their constituent parts, when they are approved or cleared under separate marketing application(s)]. The Rule does not apply to investigational combination products or to combination products that have not received marketing authorization. The Rule addresses safety reporting requirements for combination products (and when applicable, their separately marketed constituent parts) when they are approved under a NDA, ANDA, BLA, PMA or a Product Development Protocol (PDP), or cleared under a 510(k) or a Humanitarian Device Exemption (HFE). The Rule explains which post-marketing safety reports for a combination product are to be submitted to FDA and identifies records to be maintained in order to be in compliance with the regulation. The Rule becomes effective on January 19, 2017 for safety reports related to the Primary Mode of Action of a combination product. However, compliance with existing drug, biologic and medical device safety reporting rules related to the combination product's secondary mode of action (SMOA) is not required until 18 months following the Federal Register Notice.



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Summary

The Rule, codified as 21CFR4, was published as a Proposed Rule in 2009. The Final Rule contains changes that clarify that it only applies to combination product application holders (and when marketed separately, application holders for combination product constituent parts). It explains that the submission of multiple safety reports may be unnecessary when a single safety report contains sufficient information to comply with multiple safety reporting requirements required by the rule (i.e., predicate Rules, 21 CFR 310.305, 314.80, 314.98, 600.80, and 600.81 21 for drugs and biological products and 21CFR803 and 806 for medical devices). For combination product (and separately marketed device constituent parts) device-related safety reports involving deaths and serious injuries, it relaxes the submission report timing requirement from 15 days to 30 days. It requires for device containing combination products that, in order to comply with Periodic Safety Reporting (PSUR) requirements for drugs and biological products, PSURs must contain summaries of device 5-day reports malfunctions, and if a recall occurs as the result of device related serious and life-threatening device related events, compliance with Corrections and Removals regulations for medical devices is also required.

Fundamentally, combination product post-marketing safety reports are to be submitted to FDA according to rules related to the application type under which the combination product (and where applicable, its separately marketed constituent part[s]), is approved or cleared (i.e., NDA or ANDA for a product with a drug Primary Mode of Action (PMOA), BLA for a product with a biological product PMOA and PMA or 510(k) for a product with a device PMOA].

Compliance with additional reporting requirements specified in the Rule which



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are related to the constituent part(s) with a Secondary Mode of Action (SMOA) is also required.

Consistent with the approach originally outlined in the Proposed rule, the Final Rule requires holders of either an approved or cleared combination product application to comply with predicate Rules related to the marketing application and additional rules related to constituent part(s) with a SMOA. For example, for a combination product approved under a BLA or an NDA, additional 5-day reports of device malfunctions [21CFR803.50] are required and for a combination product approved under a device application, when safety-related events require the submission of 15-day “alert reports” for drugs (21CFR314.80) and biological products (21CFR600.80) and field alerts for drugs (21CFR314.81) these are also required. For biological products, the expedited Blood Fatality Report requirement (21CFR606.170) specified in the Proposed Rule is absent in the Final Rule. The Final Rule expands the required reports for combination products containing a biological product marketed under a device marketing approval or clearance by adding the requirement to comply with Biological Product Deviation Reporting requirements (BPDR, 21CFR 600.14 and 21CFR 606.171). For combination products approved under a NDA, ANDA or BLA, if a recall occurs as the result of a device-related safety event, the Rule requires compliance with Device Correction and Removal Reporting regulations (21CFR806.10). If safety reporting under 21CFR803 or 21CFR 806 is not triggered, recordkeeping requirements still apply, and under such circumstances, these requirements must be satisfied for combination products that include a device constituent part. The final Rule also requires holders of applications for separate combination product constituent parts to notify each other within 5 days of receiving information related to events specified by the Rule.



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Analysis and Comment:

The approach outlined in the Final Rule follows FDA's "streamlined" approach to regulating combination products. The streamlined approach merges postmarketing safety reporting requirements related to NDA, ANDA, BLA, PMA, PDP and 510(k) approved or cleared applications into a single regulation that references postmarketing safety reporting predicate rules. The final rule adds a few new requirements, beyond that of the predicate rules, such as the 5-day requirement to provide safety related notifications between combination product constituent part manufacturers and to align drug and device reporting of serious and life-threatening events, the Final rule also relaxes the time required to file serious or life threatening device-related safety reports from 15 days to 30 days.

The Rule only addresses how safety reports and submission timing described in predicate rules are to be applied in combination product safety reporting. The rule does not address the complex issue of the content of these reports. How safety information related to a constituent part with a SMOA is to be incorporated into safety reports related to a single application related to the PMOA of the combination product is not addressed. It is also not clear how to comply with the additional reporting requirements of the Rule when a safety related event is clearly related only to the constituent part with the PMOA.

Hopefully these questions will be addressed in anticipated guidance.