Final Rule: Post marketing Safety Reporting for Combination Products Overview

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Introduction

This final rule[1] describes the post marketing safety reporting requirements that apply when two or more different types of regulated medical products (drugs, devices, and/or biological products, which are referred to as "constituent parts") comprise a combination product where either the combination product or its constituent parts have received FDA marketing authorization. The purpose of this final rule is to ensure consistent, complete postmarketing safety reporting requirements and to avoid duplicate efforts. FDA has decided to extend the compliance date of this rule to July 2018.

Legal Authority

The legal framework underlying this final rule is twofold. The first aspect is that drugs, devices, and biological products do not lose their discrete regulatory identities when they become constituent parts of a combination product. **In general, postmarketing safety reporting requirements specific to each constituent part also apply to the combination product itself.**

The second aspect of the framework is founded on the postmarketing safety reporting regulatory scheme associated with the application under which the combination product received marketing authorization, plus any applicable requirements associated with the constituent part(s).

Understanding Combination Products and Constituent Parts Definitions

To illustrate how the combination products and constituent part definitions are used to determine who is subject to this rule, take the example of a prefilled syringe that received marketing authorization under an NDA or ANDA held by Entity A (e.g., West customer, combination product applicant), which purchases the syringe components for this product from Entity B (e.g., West), which manufactures the syringe components. **Entity A must comply with the provisions of this rule applicable to combination product applicants**. There are no constituent part applicants for the combination product.

Entity B has no reporting duties under this rule (nor does it have any under 21 CFR Part 803 or 806 for the syringe components). It bears noting that entity A is responsible not only for reporting but also for conducting any necessary quality investigations for the combination product as a whole and may need to coordinate with entity B for such investigations and to address safety issues relating to the device constituent part for the combination product.

If Entity B were also to manufacture and separately market under a 510(k) complete, finished, empty syringes, not as part of a combination product, Entity B would be subject to reporting requirements under 21 CFR Parts 803 and 806, but would not be subject to this rule for this device. Entity A would remain the sole applicant for the combination product, i.e., the combination product applicant.

Similarly, if Entity B manufactured syringes to supply to Entity A for inclusion in kits for which Entity A received marketing authorization under an NDA or ANDA. **Entity A would still be the sole applicant for the combination product**, i.e., the combination product applicant, since it holds the NDA or ANDA under

which the kits received marketing authorization, and, therefore, only Entity A would be subject to this rule.

To take another example, if Entity C receives marketing authorization under a PMA or 510(k) to market an imaging device as a **constituent part of a cross-labeled combination product**, and Entity D receives marketing authorization under an NDA or ANDA to market a contrast agent drug as a constituent part of that same cross-labeled combination product, then Entities C and D are both constituent part applicants, and both are subject to the provisions of this rule applicable to constituent part applicants. There is no combination product applicant for this product.

Postmarketing Reporting Requirements

If the combination product contains a device constituent part, the combination product applicant must submit:

- §803.53 and §803.56 - 5 Day Reports, §803.50 and §803.56 Malfunction Reports and 21 CFR Part 806 Correction or Removals Reports and Records.
- In addition to the combination product application type requirements (ANDA/NDA: 21 CFR Part 314 or BLA: 21 CFR Part 600 and 606).

FDA has not required submission of serious injury and death reports under Part 803 for combination products that received marketing authorization under a BLA, NDA, or ANDA and that include a device constituent part, based on the premise that the requirements of §600.80 and §314.80, respectively, ensure timely reporting of such events for such combination products.

If the combination product contains a drug constituent part, the combination product applicant must submit:

- §314.81 Field Alert Reports and §314.80, 15 Day Reports, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.
- In addition to the combination product application type requirements (BLA: 21 CFR Parts 600 and 606 or Device application: 21 CFR Parts 803 and 806)

If the combination product contains a biological product constituent part, the combination product applicant must submit:

- §600.14 and §600.171 Biologic Product Deviation Report and §600.80, 15 Day Reports, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.
- In addition to the combination product application type requirements (NDA: 21 CFR Part 314 or Device application: 21 CFR Parts 803 and 806)

Table 1 and 2 below summarize the post marketing requirements for combination product and constituent part applicants.

Table 1 – Requirements for Both Constituent Part Applicants and Combination Products Applicants

Source of Post Marketing Requirement	Application Type		
	ANDA/NDA	BLA	Device Application
Part 314	X		
Part 600		X	
Part 606		X	
Part 803			X
Part 806			X

Table 2 – Additional Requirements for Combination Product Applicants

Combination Product Includes	Post Marketing Reporting Requirement	Application Type		
		ANDA/NDA	BLA	Device Application
Drug	§314.81 Field Alert Reports	Table 1	X	X
	§314.80, 15 Day Reports (Initial and Follow up)		X	X
Biologics	§600.14 and §600.171 Biologic Product Deviation Reports	X	Table 1	X
	§600.80, 15 Day Reports (Initial and Follow up)	X		X
Device	§803.53 and §803.56 - 5 Day Reports (Initial and Supplemental or Follow up)	X	X	Table 1
	§803.50 and §803.56 Malfunction Reports (Initial and Follow up)	X	X	
	Part 806 – Correction or Removals Reports and Records	X	X	

Record Keeping: For constituent part or combination product applicants, records must be maintained in accordance with the recordkeeping requirements in the applicable regulation(s) and the applicable records must be maintained for the longest time required for records under the postmarketing safety reporting regulations applicable to the product.

Labeling Considerations: A serious adverse event could trigger a requirement for submission of a 15-day report as described in §314.80 or §600.80 by a combination product applicant or a drug or biological product constituent part applicant if the event is not listed in the current FDA-approved labeling for the combination product. While this rule does not establish any labeling requirements, there is a question of what labeling is relevant to a determination of whether an adverse event is unexpected for purposes of 15-day reports described in §314.80 and §600.80, if the constituent parts of the combination product have their own labeling.

Avoiding Duplicate Efforts: FDA has clarified that if a combination product applicant submits a single report that satisfies multiple applicable reporting requirements, including all submission deadlines, for reports required to be submitted in the same manner, then the applicant does not need to submit any additional reports to satisfy those reporting requirements.

1 https://www.federalregister.gov/documents/2016/12/20/2016-30485/postmarketing-safety-reporting-for-combination-products