

Combination Products: Reporting Device Information and Malfunctions

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Learning Objectives

- Provide an overview of combination products/terminology
- Provide an overview of postmarketing safety reporting (PMSR) requirements that apply to combination products
- Understand malfunction reports
- Identify device information that should be included in combination product Individual Case Safety Reports (ICSRs)

What is a Combination Product?



- Combination product: A product comprised of two or more ***different types of medical products*** (e.g., drug and device, drug and biological product, device and biological product, or all three together)
- Examples:
 - Prefilled syringes, autoinjector, nasal spray
 - Transdermal systems or microneedle patches pre-loaded with drugs
 - Drug or biological product vials packaged with device(s)
 - Surgical kits with devices and drugs
- Combination products are assigned to a “Lead Center”



What is a “constituent part”?



- Constituent part: A drug, device, or biological product that is part of a combination product.
- Examples:

Example	Constituent Parts		
	Drug	Device	Biological Product
Prefilled Vaccine Syringe		Syringe	Vaccine
Drug-Eluting Stent	Drug coating	Stent	
First-Aid Kit	Antibiotic Ointment, Antiseptic, Pain Relievers, etc.	Gauze, Bandages, Tweezers, etc.	

Goals of Combination Product PMSR



- Complete and Consistent Reporting
- Appropriate Postmarketing Surveillance
- Avoid Unnecessary Duplicative Reporting Requirements
- Clarifying How Requirements Apply to Combination Products, not Changing Underlying Requirements

Constituent part-based PMSR Requirements



NDA, ANDA, BLA (if combination product includes a device constituent part)	BLA or device application* (if combination product includes a drug constituent part)	NDA or device application* (if combination product includes a biological product constituent part)
5-day (remedial action) reports (21 CFR 803.3, .53, .56)	Field alert reports (FARs) (21 CFR 341.81)	Biological product deviation reports (BPDRs) (21 CFR 600.14, .171)
Malfunction reports (21 CFR 803.50)	15-day (serious unexpected adverse event) reports (21 CFR 314.80) (with 30-day deadline if marketed under a device application)	15-day (serious unexpected adverse event) reports (21 CFR 600.80) (with 30-day deadline if marketed under a device application)
Correction or removal reports and records (21 CFR 806.10, 806.20)		

*Device applications = PMA, 510(k), de novo, PDP, HDE (see 21 CFR 4.101)

Other reports:

- Combination product applicants marketing under an NDA, ANDA, and BLA applicants must address 5-day and malfunction reports in periodic reports (21 CFR 314.80, 600.80).
- Combination product applicants marketing under a device application must provide additional reports only as required and specified in writing by FDA.

What is a malfunction and when is it reportable to FDA?



- Malfunction: Failure of a device constituent part or of the product as a whole to meet its performance specifications or otherwise perform as intended
- Malfunction reports required if event information:
 - reasonably suggests that the product has malfunctioned **and**
 - would be likely to cause or contribute to a death or serious injury if the malfunction were to recur
- Note that a patient event does not have to occur for a malfunction to be reportable (if recurrence could cause death or serious injury)

Combination Product Malfunctions in Context



- Malfunctions may result in medication errors (e.g., out of specification component causes autoinjector to jam and the patient missed a dose)
- Use errors may result in events described as “malfunction” (patient misunderstood Instructions for Use, and jammed the injector when priming)

Information to Include in Combination Product ICSRs



- Identify the product as a combination product in the report
- Include constituent part information, regardless of whether the constituent part was implicated in the event

What device information should I include for a combination product ICSR?



- Device-related fields that should be submitted include:
 - Suspect medical device: The device product code that most closely aligns with the device constituent part(s), as well as the device common name and/or brand name, as applicable.
 - Device problem code: FDA codes specific to device issues/failures (include for malfunction reports)

What are “product codes” and “problem codes”?



- Device Product Code: FDA three letter standardized product codes (procodes) for device types.
 - For example, piston syringes are procode FMF, nasal inhalers are procode KCO
- Device Problem Code: FDA codes specific to a device issue/ failure
 - MedDRA has also adopted codes that align with common device problem codes (~150 included in MedDRA v23.0)
 - Device problem codes should still be included for reportable malfunctions

Combination Product Case Study



- Product: BLA product consisting of one vial of biological product packaged with three device constituent parts: 1) syringe, 2) vial adapter, and 3) sterile needle
- Scenario: Healthcare provider reports that a broken needle resulted in a hemorrhage.
- Device product code:
 - Syringe, Piston – FMF
 - Needle, Hypodermic, Single Lumen – FMI
 - Vial Adapter - ONB
- Device problem code: Fracture FDA 1260
- MedDRA codes: LLT Needle issue, LLT Hemorrhage

Importance of Device Information in ICSRs



- Structured device information (product codes, model, etc.) and problem codes will enhance ability to trend and assess device issues
- Additional information (for example, MedDRA coding and narrative) clarifies how the device is implicated (failed, misused, etc.)

Challenge Question #1

An applicant receives information on an event involving its NDA-approved combination product. The event is determined to require a 15-day report but there is no identified malfunction. Which of the following information should be included in the report:

- A. Device product code**
- B. Device problem code
- C. Both A and B
- D. None of the above

Summary

- Combination product applicants are subject to PMSR requirements arising from the application type and the constituent parts
- Comprehensive combination product information in the reports is critical, including information about the constituent parts

Resources

- [Combination Product PMSR webpage](#) – Consolidated information, including examples and links to product code list
- [Postmarketing Safety Reporting for Combination Products Final Guidance](#)
- Device product codes (procodes)
 - [List of procodes for common device constituent parts of ANDA/NDA/BLA combination products](#)
 - [Full list of product codes \(procodes\)](#)
- [Device problem codes](#)

Questions?

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