US FDA Final Rule on Postmarketing Safety Reporting for Combination Products

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Overview

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- Background
- Rationale for the rule
- Who is subject to the rule
- What requirements apply to whom
- How to interpret/streamline the requirements
- What to do now
- Next Steps
- Questions, comments & assistance

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Background

- Combination products: Combine two or more of three different types of medical products (drug + device, biologic + drug, etc.)
- Types of combination products:
  - Single-entity (21 CFR 3.2(e)(1)) (e.g., prefilled syringe, transdermal patch, drug-coated stent);
  - Co-packaged (21 CFR 3.2(e)(2)) (e.g., convenience kits, surgical kits);
  - Cross-labeled (21 CFR 3.2(e)(3), (4))(e.g., certain lasers and light-activated drugs that are separately distributed but labeled for use with one another)
- Constituent parts: The medical products included in the combination product

Background cont'd

- Legal construct:
  - Constituent parts retain regulatory identities, but combination products are a distinct product category (not a drug, device, or biologic)
  - Regulatory requirements generally arise from those for drugs, devices and biologics
  - FDA has authority to develop policies to ensure effective, consistent, efficient regulation of combination products
- Premarket pathways
  - Combination products are reviewed under premarket approval pathways for drugs, devices, and biologics
  - For cross-labeled combination products, separate marketing authorizations for each constituent part may be permissible instead of a single authorization for the entire product

Key Points

- Final rule codifies which postmarketing safety reporting (PMSR) requirements apply to combination products (https://www.federalregister.gov/documents/2016/12/20/2016-30485/postmarketing-safety-reporting-for-combination-products)
- Three basic duties:
  - Reporting requirements associated with application type (e.g., NDA, BLA, PMA, 510(k)) for "combination product applicants" and "constituent part applicants"
  - Specified, additional reporting requirements associated with constituent parts for "combination product applicants"
  - Information-sharing requirements for "constituent part applicants"
- Streamlining of reporting available where consistent with efficient, effective FDA engagement
- At this time, applicants should only comply with requirements associated with application types (compliance date for other elements of rule in 18 months)
- Agency is developing draft guidance and welcomes questions and feedback

The PMSR Rule Rationale

- Key stakeholder input:
  - Need consistent PMSR requirements for combination products
  - Important to avoid unnecessarily duplicative reporting
- Goals of the rule:
  - Protect the public health by ensuring a combination products' continued safety and effectiveness once placed on the market.
  - Ensure consistent and appropriate PMSR for combination products, while enabling reporting to be as efficient as possible

Rationale cont'd

- Other considerations for approach:
  - PMSR regulations for drugs, devices, and biological products are broadly similar
  - Industry is familiar/has experience with them
  - Reporting requirements vary based in part on the characteristics of drugs, devices, and biological products
  - Clarification needed on how to comply with these existing regulations, for combination products
- Comments on proposed rule sought clarification of:
  - Who is subject to the rule
  - Which requirements apply to whom
  - How to interpret and streamline compliance with the requirements

Who is subject to the rule?

The rule applies only to two defined categories of "applicants" (holders of marketing authorizations):

- "Combination product applicants"—there is a single applicant for the combination product
- "Constituent part applicants"—there are separate applicants for the constituent parts of the combination product

What requirements apply to which applicants?

- *BOTH combination product applicants & constituent part applicants*: Comply with all PMSR associated with application type
- *ONLY combination product applicants*: ALSO comply with other postmarketing safety reporting requirements specified as applicable in the rule
- *ONLY constituent part applicants*: ALSO comply with requirements to share adverse event information with the other constituent part applicant(s)

PMSR requirements applicable to BOTH combination product & constituent part applicants

Source of PMSR Requirements	Application Type		
	ANDA. NDA	BLA	Device application*
21 CFR 314	X		
21 CFR 600		X	
21 CFR 606		X	
21 CFR 803			X
21 CFR 806			X
			* Device applications = PMA, 510(k), de novo, PDP, HDE (see 21 CFR 4.101)

Additional PMSR requirements for combination product applicants

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 reports (21 CFR 803.3, .53, .56)	Field alert reports (FARs) (21 CFR 341.81)	Biological product deviation reports (BPDRs) (21 CFR 600.14m .171)
Malfunction reports (21 CFR 803.50)	15-day reports (21 CFR 314.80) (with 30-day deadline if marketed under a device application)	15-day 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 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.		

Information-sharing requirement for constituent part applicants

- Information sharing with other constituent part applicant(s) for the combination product
- What topics:
  - Death or serious injuries, within the meaning of 21 CFR 803.3 and
  - Adverse experiences within the meaning of 21 CFR 314.80(a) or 600.80(a))
- When: within five calendar days
- Scope of this duty:
  - Forwarding information along (no need to develop a report/analysis)
  - One-time forwarding of information per event (though additional coordination may be helpful)

Other requirements

- Where to send PMSRs
  - *Combination product applicants*:
    - Individual case study reports (ICSRs): As provided in the regulation associated with application type
    - Other PMSRs: As provided in the underlying regulation (or guidance) for the report type
  - *Constituent part applications*:
    - All PMSRs: As provided in the regulation for the report type
- Recordkeeping
  - *Combination product applicants*: Retain all PMSR records for longest retention period applicable to any report type for the product
  - *Constituent part applicants*:
    - Retain all PMSR records as provided in the regulation for the report type
    - Retain records of information sharing (see 21 CFR 4.103(b)) for the longest retention period for any PMSR requirement applicable to you

How to interpret requirements

Existing interpretations of standards and definitions apply, e.g., for:

- "Caused or contributed" in 21 CFR 803.3
- "Associated with" in 21 CFR 314.80 and 600.80
- "Expected" in 21 CFR 314.80 and 600.80
  - Preamble clarifies that labelling includes labelling for each constituent part if separately labelled

Streamlining

Available for individual case study reports (ICSRs)

- Can submit consolidated ICSRs (including to satisfy 5-day, 15-day and malfunction report requirements specified in the rule) if ICSR includes all the information required for each report type and is submitted by the shortest deadline
- Correction and removal requirements can also be met through this streamlined approach
- Other PMSR types are submitted through existing, established processes (e.g., FARs to the appropriate district office), to enable efficient, effective engagement by FDA

What to do Now

At this time, comply ONLY with PMSR requirements associated with your application type (see slide 11):

- Provide complete reports addressing issues regarding the entire combination product and each constituent part as appropriate
- Use the narrative portion of the ICSR form (box H.10 of Form 3500A) as needed to ensure completeness of report

Next Steps

- FDA welcomes questions and feedback on the final rule (policy, process, technical questions to address in guidance)
- We are available to address product-specific questions
- FDA Implementation of the rule
  - Developing guidance on substantive, procedural and technical considerations for complying with this rule
  - Augmenting/updating IT systems
  - Augmenting/updating training
- Stay tuned for further information

Questions, Comments & Assistance

Office of Combination Products (OCP) is:

- Available to help resolve product-specific questions
  - PMSR compliance
  - Product classification (is it a combination product, what type?)
- The point of contact for comments and questions on this rule, as for combination product policy and practice in general
- Happy to assist with any other questions

For additional information

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