Combination Product Postmarketing Safety Reporting Requirements Implementation Update

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Topics

- Summary of Combination Product Postmarketing Safety Reporting (PMSR) Requirements and Implementation
- Highlight recurring inquiries/topics

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Summary of PMSR

- Application-based reporting requirements apply BOTH to Combination Product Applicants and Constituent Part Applicants:
- Constituent part-based reporting requirements (next slide) apply ONLY to Combination Product Applicants
- Information-sharing requirements apply to Constituent Part Applicants (generally, applicants for cross-labeled combination products)
- Lead Center procedural requirements apply for ICSRs (e.g., CDER-led are submitted to FAERS)
- Streamlining is available: Multiple ICSRs (e.g., Fifteen day and Malfunction submitted in one report), submitted by the shortest deadline

Combination Product PMSR requirements are in effect for combination products (except vaccines) as of **July 31, 2020**

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Constituent part-based 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.		

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FDA Preparation

- IT systems for ICSRs have been updated
- Staff have been trained on combination product PMSR requirements and information included in reports
- Plan to conduct ongoing assessment of information received and center coordination on PMSR issues

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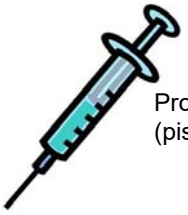
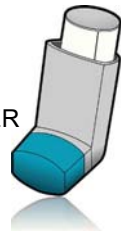
Device Constituent Part Information

- Include constituent part information in ICSRs, regardless of whether the constituent part was implicated in the event
- Suspect medical device: Device product code, as well as the device common name and/or brand name, as applicable
  - List of procodes for common device constituent parts of ANDA/NDA/BLA combination products on FDA website
  - FDA has added procodes to cover some CDER and CBER-led products



Procode FMF (piston syringes)



Procode QKS (metered dose inhaler for CBER or CDER-led)

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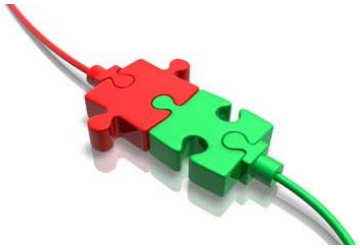
Device Constituent Part Information, cont.

- Device Problem Code: FDA codes for device issue/failure
  - eMDR accepts harmonized codes (e.g., IMDRF). FAERS submitters should continue to use the FDA problem code format
  - Although MedDRA has codes that align with problem codes, ICSRs should include FDA device problem code
  - List of Problem Codes on the FDA Website



- Questions on use of device product codes/problem codes, contact us: combination@fda.hhs.gov

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Reporting for "Same or Similar" Device Constituent Parts

- Submit malfunction reports for otherwise reportable malfunctions for devices and device constituent parts of combination products marketed outside the U.S. by the applicant that:
  - Are the same as or similar to device constituent part of the U.S.-marketed combination product
  - Malfunction is likely to occur in U.S.-marketed combination product

- Drug characterization role of "Similar" added to FAERS

B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1=Suspect 2=Concomitant 3=Interacting 5=Similar	If the product in the report is about a similar device, the element value should be 5=Similar Device.

See Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

  - FAERS Example Scenarios for Same or similar device constituent parts

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Recurring Inquiries/Topics

- Five-day Reports generally should be submitted as a separate report due to public health significance (see PMSR guidance footnote 29)

Table 2. Detailed Description of Administrative Tags*

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
A.1.9	<fulfillexpeditecriteria>	1N	1= Yes (15-Day expedited) 2= No (non-expedited) 4= 5-Day 5= 30-Day 6= 7-Day expedited

See Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

- Five-day and malfunction report information must now be included in periodic reports

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Recurring Inquiries/Topics, cont.

- Combination Product Applicant must assess information of which they become aware
  - Including information from studies (investigational use, postmarket studies, etc.) that involve a marketed combination product
  - Direct questions on investigational combination product reporting to combination@fda.hhs.gov, as needed

- VAERS system for vaccine reporting has been updated, implementation date for requirements is January 31, 2021
  - See CBER Vaccine ICSR Implementation for information and examples

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Closing Thoughts

- Comprehensive combination product information in the report is critical
- Combination product PMSR requires integration across disciplines / functional areas (e.g., quality and safety)
- We are available for questions: combination@fda.hhs.gov

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Resources

- Combination Product PMSR webpage – Consolidated information and links, including:
  - Postmarketing Safety Reporting for Combination Products Final Guidance
  - Examples
  - Links to Technical Information on Reporting Systems (FAERS, eMDR, VAERS)
  - Links to product code information

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