

# **Compliance Policy for Combination Product Postmarketing Safety Reporting**

## **Immediately in Effect Guidance for Industry and Food and Drug Administration Staff**

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Office of Combination Products (OCP)  
Center for Biologics Evaluation and Research (CBER)  
Center for Drug Evaluation and Research (CDER)  
Center for Devices and Radiological Health (CDRH)**

**March 2018**

# Compliance Policy for Combination Product Postmarketing Safety Reporting Immediately in Effect Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. Introduction

This guidance document is intended to assist Combination Product Applicants who are subject to the Combination Product Postmarketing Safety Reporting Final Rule (hereafter “combination product PMSR final rule,” “final rule,” or “rule”), issued on December 20, 2016 (81 FR 92603), and codified in 21 CFR Part 4, Subpart B. This guidance document discusses FDA’s compliance policy for the rule. FDA does not intend to enforce certain requirements under the rule, specifically 21 CFR 4.102(c) and (d), 4.104(b)(1) and (b)(2), and 4.105(b), for a period of time as discussed further in section III below. FDA intends to delay enforcement of these provisions to ensure that Combination Product Applicants have sufficient time to update reporting and recordkeeping systems and procedures, including their information technology systems, to comply with these requirements, and in doing so, have sufficient time to consider the recommendations and technical specifications that FDA intends to provide through guidance to support compliance. For all other provisions of 21 CFR Part 4, Subpart B, FDA intends to enforce (or continue enforcing) the requirements per its usual policies as of the compliance date provided in the final rule.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

## II. Background

In the Federal Register of December 20, 2016 (81 FR 92603), FDA published a final rule for postmarketing safety reporting (PMSR) for combination products as defined at 21 CFR 3.2(e). The combination product PMSR final rule applies to combination products that are subject to premarket review by FDA. The entities subject to the final rule are “Combination Product Applicants,” which are applicants that hold the only application for a combination product or all

the applications for the “constituent parts” (drug, device, or biological product) of a combination product, and “Constituent Part Applicants,” which are applicants for a constituent part of a combination product the constituent parts of which are marketed under applications held by different applicants (see 21 CFR 4.100 and 4.101).

Under the final rule, Combination Product Applicants must comply with: application type-based PMSR requirements (PMSR requirements associated with the application type under which the combination product received marketing authorization) (see 21 CFR 4.102(a) and (b)), constituent part-based PMSR requirements (specified in the rule based on the types of constituent parts included in the combination product) (see 21 CFR 4.102(c) and (d)), and associated submission process and recordkeeping requirements (see 21 CFR 4.104(b) and 4.105(b)).

In the preamble to the final rule (81 FR at 92619), FDA stated that the compliance date for the application type-based PMSR requirements for Combination Product Applicants and Constituent Part Applicants under 21 CFR 4.102(a) and (b), and for the submission process and recordkeeping requirements for Constituent Part Applicants under 21 CFR 4.104(a) and 4.105(a)(1), respectively, was the same as the effective date for the final rule (January 19, 2017). These requirements are generally the same as for any other entity holding such an application for its product, and we expected all applicants subject to this rule to already be in compliance with these provisions as such provisions generally refer to existing regulations that such applicants have generally followed. With respect to the PMSR requirements of 21 CFR 4.102(c) and (d), 4.103, 4.104(b), and 4.105(a)(2) and (b), the final rule established a compliance date 18 months following the effective date of the rule (i.e., compliance date of July 19, 2018).

### **III. FDA's Compliance Policy for the Combination Product PMSR Final Rule**

FDA does not intend to enforce the following provisions of the combination product PMSR final rule applicable to Combination Product Applicants prior to the dates provided in the bullets below: 21 CFR 4.102(c) and (d) (constituent part-based PMSR requirements), 4.104(b)(1) and (b)(2) (submission process for constituent part-based Individual Case Safety Reports (ICSRs)<sup>1</sup>), and 4.105(b) (recordkeeping requirements).

- July 31, 2019, for Combination Product Applicants using the FDA Adverse Event Reporting System (FAERS) and Electronic Medical Device Reporting System (eMDR) to report ICSRs.
- January 31, 2020, for Combination Product Applicants using the Vaccine Adverse Event Reporting System (VAERS) to report ICSRs.

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<sup>1</sup> The term “Individual Case Safety Report” (ICSR) is used to describe a report of an event experienced by an individual user of a combination product, including adverse events and malfunctions. For purposes of the combination product PMSR final rule and this guidance, ICSRs encompass Fifteen-day reports (see 21 CFR 314.80, 600.80), Five-day reports (see 21 CFR 803.3, 803.53, 803.56), Malfunction reports (see 21 CFR 803.50, 803.56), and death or serious injury reports (21 CFR Part 803).

FDA intends to delay enforcement of the above provisions to ensure that Combination Product Applicants have sufficient time to update reporting and recordkeeping systems and procedures, including their information technology systems, to comply with these requirements. During the period of delayed enforcement, FDA intends to focus on educating Combination Product Applicants on the above provisions with which they may be less familiar, including providing guidance to help them comply with these provisions. The period of delayed enforcement will provide Combination Product Applicants with additional time to consider the recommendations and technical specifications that FDA intends to provide through the aforementioned guidance as they update their systems and procedures to comply with these provisions.

For all other provisions of 21 CFR Part 4, Subpart B, FDA intends to enforce the requirements per its usual policies<sup>2</sup> as of the compliance date provided in the final rule. Specifically, FDA intends to continue enforcing the requirements under 21 CFR 4.102(a) and (b) (application type-based safety reporting requirements for Combination Product Applicants and Constituent Part Applicants), 4.104(a) (submission process requirements for Constituent Part Applicants), and 4.105(a)(1) (recordkeeping requirements for Constituent Part Applicants) (the compliance date for these provisions was January 19, 2017), and intends to enforce the requirements under 21 CFR 4.103 (information sharing requirements for Constituent Part Applicants) and 4.105(a)(2) (recordkeeping requirements for information shared with Constituent Part Applicants) starting on July 19, 2018 (which is the compliance date for these provisions) because FDA does not believe significant updates to systems and procedures are necessary to comply with these provisions.

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<sup>2</sup> FDA's usual enforcement policies would apply in deciding whether to take enforcement action for violations in any given case, including the consideration of numerous factors such as whether the Agency's resources would be best spent on a particular case.

# Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff

## *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit written or electronic comments on the draft guidance within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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**U.S. Department of Health and Human Services  
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Center for Biologics Evaluation and Research (CBER)  
Center for Drug Evaluation and Research (CDER)  
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**March 2018**

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# Guidance for Industry and FDA Staff: Postmarketing Safety Reporting for Combination Products

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## I. Introduction

This guidance addresses how to comply with the final rule on postmarketing safety<sup>1</sup> reporting (PMSR) requirements for combination products that FDA issued on December 20, 2016 (81 FR 92603, hereafter the “combination product PMSR final rule,” “final rule,” or “rule”). The rule describes how to comply with PMSR requirements for combination products that have received FDA marketing authorization. Although the PMSR regulations for drugs, devices, and biological products share many similarities, each set of regulations establishes distinct reporting requirements, including reporting triggers and timeframes. The final rule addresses the application of these regulatory requirements to combination products to ensure consistent and complete reporting while avoiding duplication.

Section II of the guidance provides general information on combination products, how FDA regulates combination products, and a summary of the combination product PMSR final rule. Section III provides an overview of which entities are subject to the final rule and what safety reporting requirements apply to such entities. Section IV provides more detailed discussion of specific combination product PMSR report types. Section V provides guidance on where, how, and when to submit PMSR reports to FDA. Section VI provides hypothetical scenarios that illustrate how to comply with certain combination product PMSR requirements. While this guidance focuses on the requirements of the combination product PMSR final rule, it also addresses associated topics including postmarketing safety reporting requirements applicable to entities not covered by the rule (see Appendix 3).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

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<sup>1</sup> As described in the combination product PMSR final rule, the term “postmarketing safety” is used because the rule concerns certain postmarket events, including manufacturing events, malfunctions, and events causing injury to users, and the reporting requirements relating to product and patient safety that arise from these events. The final rule supports the underlying purpose of postmarketing safety reporting for all medical products, namely to protect the public health by ensuring continued safety and effectiveness of the product after it is placed on the market.

36 requirements are cited. The use of the word “should” in agency guidance documents means that  
37 something is suggested or recommended, but not required.

## 38 **II. Background**

### 39 **A. What is a combination product?**

40 A combination product is a product comprised of any combination of a drug, a device, and a  
41 biological product.<sup>2</sup> Each drug, device, and biological product included in a combination  
42 product is referred to as a “constituent part” of the combination product.

43  
44 Under 21 CFR 3.2(e), a combination product includes:

- 45  
46 • A product comprised of two or more regulated components, i.e., drug/device,  
47 biologic/device, drug/biologic, or drug/device/biologic, that are physically,  
48 chemically, or otherwise combined or mixed and produced as a single entity.  
49 Examples of “single entity” combination products include a prefilled syringe or drug-  
50 eluting stent.
- 51  
52 • Two or more separate products packaged together in a single package or as a unit and  
53 comprised of drug and device products, device and biological products, or biological  
54 and drug products. Examples of “co-packaged” combination products include  
55 surgical and first-aid kits.
- 56  
57 • A drug, device, or biological product packaged separately that according to its  
58 investigational plan or proposed labeling is intended for use only with an approved  
59 individually specified drug, device, or biological product where both are required to  
60 achieve the intended use, indication, or effect and where upon approval of the  
61 proposed product the labeling of the approved product would need to be changed,  
62 e.g., to reflect a change in intended use, dosage form, strength, route of  
63 administration, or significant change in dose. A light-emitting device that is intended  
64 for use with a specific light-activated drug may be an example of such a “cross-  
65 labeled” combination product.
- 66  
67 • Any investigational drug, device, or biological product packaged separately that  
68 according to its proposed labeling is for use only with another individually specified

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<sup>2</sup> During FDA’s existing premarket review process, applicants are typically informed that their product is a combination product or a constituent part of a combination product as defined in 21 CFR Part 3. If you are uncertain of whether your product is a combination product or a constituent part of a combination product, we encourage you to contact the Office of Combination Products (OCP). If you wish to obtain a binding classification determination from FDA, you may submit a request for designation to OCP (See Guidance for Industry, *How to Write a Request for Designation (RFD)*, at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm>), or if you wish to obtain informal feedback on the classification of your product, you may submit a “Pre-RFD” (See Guidance for Industry, *How to Prepare a Pre-Request for Designation (Pre-RFD)*, at <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM534898.pdf>).



69           investigational drug, device, or biological product where both are required to achieve  
70           the intended use, indication, or effect (another basis for cross-labeled combination  
71           product status).

## 72           **B. How does FDA review and regulate combination products?**

73           A combination product is assigned to an Agency center that will have primary jurisdiction (i.e.,  
74           the “lead Center”) for that combination product’s premarket review and regulation. Under  
75           section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C.  
76           353(g)(1)), assignment of a combination product to a lead Center is based on a determination of  
77           which constituent part provides the primary mode of action (PMOA) of the combination  
78           product.<sup>3</sup>

79  
80           If, for example, the PMOA of a device-biological product combination product is attributable to  
81           the biological product, the center responsible for premarket review of such a biological product  
82           would have primary jurisdiction for the regulation of the combination product. The lead Center  
83           for premarket review of the combination product also has the lead for ensuring compliance with  
84           postmarket regulatory requirements. Regardless of the PMOA, Agency components will  
85           coordinate as appropriate to ensure efficient, effective, and appropriately consistent PMSR  
86           policies and review of PMSR information. For combination product PMSR, the lead Center will  
87           coordinate review of PMSR information and responses to the submitter with the other center(s)  
88           and the Office of Combination Products (OCP), as appropriate in light of the issues raised and  
89           expertise needed.

## 90           **C. Summary of the Combination Product PMSR Final Rule**

91           The combination product PMSR final rule addresses combination products that are subject to  
92           premarket review by FDA. The entities subject to the final rule are “Combination Product  
93           Applicants” and “Constituent Part Applicants” (See section III.A below for additional  
94           explanation of these two categories of entities). Major provisions of the final rule are:

- 95  
96           • Application Type-Based Reporting Requirements. These requirements apply to *both*  
97           Combination Product Applicants and Constituent Part Applicants, based on the  
98           application type under which the combination product or constituent part received  
99           marketing authorization. (See section III.B.1 for more detailed discussion of application  
100           type-based reporting requirements.)
- 101           • Constituent Part-Based Reporting Requirements and Streamlining Options. These  
102           additional reporting requirements apply *only* to Combination Product Applicants, based

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<sup>3</sup> The “primary mode of action” is the single mode of action (drug, device, or biological product) of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product (21 USC 353(g)(1)(C), see 21 CFR 3.2(m)) (21 CFR 3.2(k) (defines “mode of action” and “therapeutic”)). For more information on product classification, assignment, and PMOA, see Guidance for Industry, [How to Write a Request for Designation \(RFD\)](https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf), at <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf>.

103 on the types of constituent parts included in the combination product. (See sections  
104 III.B.2 and IV below for detailed discussion of these requirements.)

105 • Information Sharing. The rule requires Constituent Part Applicants to share certain  
106 postmarketing safety information they receive with one another. (See section IV.D below  
107 for detailed discussion.)

108 • Submission Process for Combination Product PMSR Information. The rule specifies how  
109 Combination Product and Constituent Part Applicants must submit PMSR information to  
110 the Agency. (See section V.A for detailed discussion of how to submit information to the  
111 Agency.) The rule enables applicants to submit a single report to satisfy multiple  
112 reporting requirements if all the information to be reported can be submitted in the same  
113 manner and the report satisfies all applicable reporting requirements, including all  
114 submission timelines. (See section IV.C below regarding combining reports.)

115 • Records Retention. The rule specifies what records Combination Product and  
116 Constituent Part Applicants must maintain and how long to maintain them. (See section  
117 IV.E below for detailed discussion.)

### 118 **III. General Considerations for Combination Product PMSR** 119 **Compliance**

#### 120 **A. Who is subject to the Combination Product PMSR Final Rule?**

121 The combination product PMSR final rule applies to two types of “applicants,” Combination  
122 Product Applicants and Constituent Part Applicants.<sup>4</sup> These terms and the related terms,  
123 “applicant” and “application” are defined at 21 CFR 4.101.  
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<sup>4</sup> There are other combination product entities involved with the manufacture and distribution of combination products that are not “applicants” and, therefore, not subject to the combination product PMSR final rule, but who have postmarketing safety reporting obligations under FDA’s regulations and the FD&C Act. Postmarketing safety reporting for such entities is addressed in Appendix 3.

Also, although investigational combination products are not subject to the combination product PMSR final rule, if the combination product in the clinical investigation or one of the constituent parts of an investigational combination product is already legally marketed, any adverse events associated with the marketed combination product or constituent part in the investigational setting must be reported as required by the PMSR requirements that apply to that marketed combination product or constituent part. See related discussion of use of marketed products in clinical investigations in Guidance for Industry and Food and Drug Administration Staff, [Medical Device Reporting for Manufacturers](https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm359566.pdf) (<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm359566.pdf>) and Guidance for Industry and Investigators, *Safety Reporting Requirements for INDs and BA/BE Studies* (<https://www.fda.gov/downloads/Drugs/Guidances/UCM227351.pdf>).

Entities with questions regarding how to comply with reporting requirements applicable to non-applicants or investigational combination products should contact the lead Center or OCP, as needed.

*Contains Nonbinding Recommendations*  
*Draft — Not for Implementation*

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- Applicants and Applications. Applicant means “a person holding an application under which a combination product or constituent part of a combination product has received marketing authorization (such as approval, licensure, or clearance).” Applications under this rule are: New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Biologics License Applications (BLAs) and “Device Applications”<sup>5</sup> (Premarket Approval Applications (PMAs), Product Development Protocols (PDPs), Humanitarian Device Exemptions (HDEs), De Novo Classification Requests (De Novos), and Premarket Notification Submissions (510(k)s)).
  - A Combination Product Applicant holds the only application or all applications for a combination product. For example, the following would be Combination Product Applicants:
    - A company that holds an approved PMA for a drug-eluting stent (a single entity combination product).
    - A company that holds an approved NDA for a metered-dose inhaler co-packaged with a filled drug product cartridge (a co-packaged combination product).
    - A company that holds an approved BLA for a vaccine supplied as a pre-filled syringe (a single entity combination product).
    - A company that holds both an approved PMA for a laser system that is indicated for photoactivation of a specific drug *and* an approved NDA for the specific drug that requires photoactivation by that laser system (which comprise a cross-labeled combination product).
  - A Constituent Part Applicant holds an application for a constituent part of a combination product, the other constituent part(s) of which is marketed under an application held by a different applicant. For example, where a laser system (device) and light-activated drug comprise a cross-labeled combination product (see 21 CFR 3.2(e)), the following would be Constituent Part Applicants:
    - The entity that holds the approved PMA for the laser system.
    - The separate entity that holds the approved NDA for the light-activated drug.

156 In summary, if one company is the applicant for a combination product that is marketed under a  
157 single application (e.g., a drug-eluting stent), then this entity is the Combination Product  
158 Applicant, and there are no Constituent Part Applicants for the product. Similarly, if one  
159 company holds the two applications to market two products for use together that are constituent  
160 parts of a combination product (e.g., the company holds both the NDA for a specific  
161 photoactivated drug and the PMA for a device used to activate that drug where the two products  
162 comprise a cross-labeled combination product), then that company is the Combination Product  
163 Applicant, and there are no Constituent Part Applicants. If, instead, one entity holds the NDA  
164 for the drug constituent part and a separate entity holds the PMA for the device constituent part  
165 of that cross-labeled combination product, those two entities would be the Constituent Part  
166 Applicants for that combination product, and there would be no Combination Product Applicant  
167 for that product.

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<sup>5</sup> 21 CFR 4.101.

169 It is important to note that a company that holds an application for a product is a Constituent Part  
170 Applicant *only if that entity holds an application to market that product as a constituent part of a*  
171 *combination product*. For example, SyringeCo holds a 510(k) for a general-use syringe for  
172 injection and markets empty syringes under this 510(k). PharmaCo purchases syringes from  
173 SyringeCo and includes them with drug product vials in a co-packaged combination product for  
174 which PharmaCo holds the approved NDA. Because SyringeCo does *not* hold an application  
175 under which the syringe is marketed as a constituent part of a combination product, SyringeCo is  
176 *not* a Constituent Part Applicant for a combination product.<sup>6</sup> Rather, PharmaCo is *the*  
177 Combination Product Applicant for the co-packaged combination product, and there are *no*  
178 Constituent Part Applicants for the combination product.<sup>7</sup>

179 **B. What safety reporting requirements apply to me if I am a**  
180 **Combination Product Applicant or Constituent Part Applicant?**

181 This section summarizes what safety reporting requirements associated with the constituent parts  
182 of a combination product (i.e., 21 CFR Part 314 for drugs, 21 CFR Parts 600 and 606 for  
183 biological products, and 21 CFR Parts 803 and 806 for devices) apply to Combination Product  
184 and Constituent Part Applicants under the combination product PMSR final rule, and the  
185 information sharing requirements that apply to Constituent Part Applicants under the rule.<sup>8</sup>  
186 (Appendix 1 provides a summary table of the PMSR requirements applicable to the various types  
187 of Combination Product and Constituent Part Applicants. See also section IV for additional  
188 discussion of the PMSR requirements specified in the rule for Combination Product Applicants.)

189 ***1. Application type-based reporting requirements apply to BOTH Combination***  
190 ***Product Applicants and Constituent Part Applicants***

191 *Both* Combination Product Applicants and Constituent Part Applicants must meet the safety  
192 reporting requirements associated with the application type under which the combination product  
193 or constituent part received marketing authorization. Under 21 CFR 4.102(b), Combination  
194 Product and Constituent Part Applicants who hold:

- 195
- 196 • NDAs/ANDAs are subject to the safety reporting requirements described in 21 CFR Part  
197 314
  - 198
  - 199 • BLAs are subject to the safety reporting requirements described in 21 CFR Parts 600 and  
200 606
- 201

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<sup>6</sup> SyringeCo would have its own postmarketing safety reporting obligations that apply to its device.

<sup>7</sup> Although outside the scope of this guidance, it is worth noting that, under this example, PharmaCo is required to establish and maintain procedures to ensure that supplied syringes meet all required specifications (see 21 CFR Part 4, Subpart A and Guidance for Industry and FDA Staff, [Current Good Manufacturing Practice Requirements for Combination Products](https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm429304.pdf) (<https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm429304.pdf>)).

Purchasing controls should include, for example, appropriate provisions to allow communications and information sharing between SyringeCo and PharmaCo when necessary to investigate adverse events that involve the syringe.

<sup>8</sup> There are provisions on exemptions, alternatives, and waivers under some of the PMSR regulations (see, e.g., 21 CFR 314.90, 600.90, and 803.19). These provisions apply to combination products. Questions about requesting exemptions, alternatives, or waivers should be directed to the lead Center or OCP, as needed.

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- 202       • Device Applications are subject to the safety reporting requirements described in 21 CFR  
203       Parts 803 and 806

204                   **2. Constituent part-based reporting requirements apply ONLY to Combination**  
205                   **Product Applicants**

206 In addition to application type-based reporting requirements, *only* Combination Product  
207 Applicants are also subject to certain safety reporting requirements associated with the  
208 constituent parts of the combination product (see 21 CFR 4.102(c)). Listed below are the  
209 additional reporting requirements Combination Product Applicants must meet based on the  
210 constituent parts of the combination product, for various application types (and discussed in  
211 more detail in section IV below, including streamlining opportunities):  
212

- 213       • NDA/ANDA/BLA for a combination product that contains a device constituent part. The  
214       Combination Product Applicant must also comply with:  
215           ○ Five-day reporting requirements (see 21 CFR 803.3, 803.53, and 803.56)  
216           ○ Malfunction reporting requirements (see 21 CFR 803.50 and 803.56)  
217           ○ Correction or removal reporting and recordkeeping requirements for events that  
218           do not require a report (see 21 CFR 806.10 and 806.20)  
219
- 220       • BLA or Device Application for a combination product that contains a drug constituent  
221       part. The Combination Product Applicant must also comply with:  
222           ○ Field alert reporting requirements (see 21 CFR 314.81)  
223           ○ Fifteen-day reporting requirements (see 21 CFR 314.80<sup>9</sup>)  
224
- 225       • ANDA/NDA or Device Application for a combination product that contains a biological  
226       product constituent part. The Combination Product Applicant must also comply with:  
227           ○ Biological product deviation reporting requirements (see 21 CFR 600.14 and  
228           606.171)  
229           ○ Fifteen-day reporting requirements (see 21 CFR 600.80)  
230

231 If instead of marketing a combination product under a single application, a Combination Product  
232 Applicant markets the constituent parts of the combination product under separate applications,  
233 then under 21 CFR 4.102(b), the Combination Product Applicant must comply with the PMSR  
234 requirements associated with each application type. The Combination Product Applicant would  
235 appropriately meet the reporting requirements in 21 CFR 4.102(b) by reporting separately for  
236 each constituent part in accordance with the requirements associated with the application type for  
237 that constituent part. Such reports should address how the event is related to the constituent part  
238 and the combination product as a whole.

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<sup>9</sup> The reporting requirements are aligned between 21 CFR 314.80 and 600.80, and combination products with both drug and biological product constituent parts need not submit a Fifteen-day report twice. Submitting a single Fifteen-day report containing the required information is sufficient (see also section IV.A.1).

239 **3. Information sharing requirements apply ONLY to Constituent Part Applicants**

240 Constituent Part Applicants must share with the other Constituent Part Applicant(s) for the  
241 combination product, within 5 calendar days from initial receipt, information on the following if  
242 associated with the use of the combination product:

- 243
- 244 • Deaths or serious injuries as described in 21 CFR 803.3, or
- 245
- 246 • Adverse experiences as described in 21 CFR 314.80(a) or 600.80(a).
- 247

248 See 21 CFR 4.103.

249 **IV. Specific PMSR Requirements**

250 This section discusses specific PMSR requirements in greater detail. Sections IV.A and IV.B  
251 describe the constituent part-based reports that Combination Product Applicants are required to  
252 submit (see 21 CFR 4.102). Section IV.C describes means to streamline reporting (see 21 CFR  
253 4.102). Section IV.D describes information sharing requirements for Constituent Part Applicants  
254 (see 21 CFR 4.103), and Section IV.E describes recordkeeping requirements (see 21 CFR 4.105).  
255 (The process requirements for submitting reports under 21 CFR 4.104 are addressed in section  
256 V.)

257

258 In sections IV.A and IV.B, we describe each report type with examples to illustrate combination  
259 product considerations, and we refer to additional resources that may be helpful to Combination  
260 Product Applicants. The discussion is not meant to provide comprehensive analysis of the  
261 reporting requirements for Combination Product Applicants but rather to help Combination  
262 Product Applicants understand PMSR requirements not associated with the application type for  
263 their combination product, with which they may be less familiar, and to highlight considerations  
264 specific to combination products for complying with PMSR requirements.<sup>10</sup> Note that 21 CFR  
265 4.102(a) establishes that, for Combination Product Applicants, the safety reporting requirements  
266 under 4.102(b) based on the application type and under 4.102(c) based on the constituent parts of  
267 the combination product, apply to the combination product as a whole. This means that these  
268 safety reporting requirements apply to the entire combination product. For clarity, adjustments  
269 have been made in the discussion of these requirements, such as using the term “product” in  
270 place of the term “drug,” “biological product,” or “device.”

271 **A. Individual Case Safety Reports**

272 Throughout this guidance the term “Individual Case Safety Report” (ICSR) is used to describe a  
273 report of an event experienced by an individual user of a combination product, including adverse  
274 events and malfunctions. For purposes of the combination product PMSR final rule and this  
275 guidance, ICSRs encompass Fifteen-day reports (see 21 CFR 314.80 and 600.80), Five-day

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<sup>10</sup> Because it is expected that Constituent Part Applicants are already familiar with the reporting regulations applicable to their product type (drug, device, or biological product), reporting considerations specifically for Constituent Part Applicants are not a focus of the discussion.

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276 reports (see 21 CFR 803.3, 803.53, and 803.56), Malfunction reports (see 21 CFR 803.50 and  
277 803.56), and death or serious injury reports (see 21 CFR Part 803).

278  
279 Note that death and serious injury reporting requirements (see 21 CFR Part 803) are not  
280 discussed below because, under the combination product PMSR final rule, they apply only to  
281 Combination Product and Constituent Part Applicants who are marketing their product under a  
282 Device Application, and these applicants are expected to be familiar with these application type-  
283 based reporting requirements. Similarly, we are not addressing the reporting of non-expedited  
284 (non-15-day) ICSRs under 21 CFR 314.80 and 600.80 because these requirements apply only to  
285 Combination Product and Constituent Part Applicants who are marketing their product under an  
286 ANDA, NDA, or BLA, and these entities are expected to be familiar with these application type-  
287 based reporting requirements.

288  
289 Please note that each of the sections below discusses circumstances under which the specified  
290 report type may be required. These discussions are not intended to identify all reports that may  
291 be required for the events described, and different reports may be required for similar events to  
292 those described depending on the specific circumstances. As indicated below, in some cases,  
293 multiple report types may be required, and it may be possible to satisfy multiple reporting  
294 requirements in the same submission as discussed more fully in section IV.C and section V.A.3  
295 below.

296  
297 (Appendix 2 presents flowcharts illustrating how to determine whether ICSRs must be submitted  
298 by Combination Product Applicants.)

299 ***1. Fifteen-day reports (see 21 CFR 314.80 and 600.80)***<sup>11</sup>

300 For combination products that contain a drug or biological product constituent part, the  
301 Combination Product Applicant is required to submit Fifteen-day reports (see 21 CFR  
302 4.102(b)(2) and (b)(3) and 4.102(c)(2)(ii) and (c)(3)(ii)).<sup>12</sup> Fifteen-day reports must be  
303 submitted for “adverse experiences” that are both “serious” and “unexpected” within fifteen  
304 calendar days (see 21 CFR 314.80(a) and (c) and 600.80(a) and (c)) or within 30 calendar days  
305 for combination products marketed under a Device Application as explained below.<sup>13</sup>  
306

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<sup>11</sup> 21 CFR 314.80(c) and 600.80(c) use the term “15-day Alert reports.” In the combination product PMSR final rule (see 21 CFR 4.101), these reports are defined as “Fifteen-day reports” and this term will be used throughout this guidance.

<sup>12</sup> When considering submission of a Fifteen-day report to FDA, at a minimum, applicants should have knowledge of the following four data elements: 1) an identifiable patient, 2) an identifiable reporter, 3) a suspect product, and 4) an adverse experience. For additional information, see Draft Guidance for Industry, *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines* (<https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm092257.pdf>) which, when final, will represent the FDA’s current thinking on this topic.

<sup>13</sup> For additional information on these definitions, refer to the Draft Guidance for Industry, *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines* (<https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074850.htm>) which, when final, will represent the Agency’s current thinking on this topic.

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- 307
- 308 • Adverse experience. An *adverse experience* is any adverse event associated with the use  
309 of the combination product, whether or not considered related to the product.<sup>14</sup>
  
  - 310 • Seriousness. A *serious adverse experience* is any adverse experience that results in any  
311 of the following outcomes: Death, a life-threatening adverse experience, inpatient  
312 hospitalization or prolongation of existing hospitalization, a persistent or significant  
313 disability/incapacity, or a congenital anomaly/birth defect. Important medical events that  
314 may not result in death, be life-threatening, or require hospitalization may be considered  
315 a serious adverse experience when, based upon appropriate medical judgment, they may  
316 jeopardize the patient or subject and may require medical or surgical intervention to  
317 prevent one of the aforementioned outcomes. (see 21 CFR 314.80(a) and 600.80(a).)
  
  - 318
  - 319 • Unexpectedness. An *unexpected adverse experience* is any adverse experience that is  
320 not listed in the current labeling for the product. This includes events that may be  
321 symptomatically and pathophysiologically related to an event listed in the labeling, but  
322 differ from the event because of greater severity or specificity. (see 21 CFR 314.80(a)  
323 and 600.80(a).) Whether an event is “expected” for purposes of Fifteen-day reporting is  
324 based on whether the event is listed in any current labeling for the combination product  
325 including the labeling accompanying each of the constituent parts. For example, if a  
326 Combination Product Applicant is marketing a cross-labeled combination product, the  
327 labeling accompanying each of the constituent parts would collectively constitute the  
328 labeling for the combination product.

329

330 Combination Product Applicants must submit Fifteen-day reports as described in 21 CFR 314.80  
331 and 600.80 for all serious and unexpected adverse experiences with the combination product.  
332 For example, consider a combination product approved under an NDA that contains a delivery  
333 device used to insert the drug constituent part into the body. If the delivery device breaks during  
334 drug delivery, causing the patient to hemorrhage and be hospitalized to surgically remove the  
335 device fragments, the Combination Product Applicant must submit a Fifteen-day report because  
336 hemorrhage is both a serious and unexpected adverse experience associated with the use of the  
337 combination product.

338

339 Combination products under Device Applications. For combination products marketed under a  
340 Device Application, Fifteen-day reports must be submitted within 30 calendar days, rather than  
341 fifteen. If the Combination Product Applicant for such a combination product receives a report  
342 of an event that qualifies for reporting both as a death or serious injury report under 21 CFR Part  
343 803 and as a Fifteen-day report because the event is unexpected, the Combination Product  
344 Applicant may satisfy both reporting requirements by submitting a single report that is identified  
345 both as a death or serious injury report and as a Fifteen-day report, within the 30-calendar day  
346 submission timeline. This report must include the content required for both types of reports (see  
347 sections IV.C, V.B.1, and V.B.2 below for further discussion).

348

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<sup>14</sup> As described in 21 CFR 314.80(a) and 600.80(a), adverse experiences include any failure of expected pharmacological action and adverse events occurring in the course of the use of the product in professional practice, from product overdose whether accidental or intentional, from product abuse, or from product withdrawal, and .



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349 A Combination Product Applicant for a combination product marketed under a Device  
350 Application may receive a report of an event that triggers a Fifteen-day report but not a death or  
351 serious injury report under 21 CFR Part 803, if the event is associated with the use of the  
352 combination product but the applicant does not believe the information reasonably suggests that  
353 the product may have caused or contributed to the event. FDA anticipates that such  
354 circumstances would be rare, but should they arise and the event is both a serious and  
355 unexpected adverse experience, the Combination Product Applicant must submit a Fifteen-day  
356 report even though a death or serious injury report is not also required.

357  
358 Combination products that contain a drug and biological product. A Combination Product  
359 Applicant for a combination product that contains both a drug and biological product constituent  
360 part need not submit two separate Fifteen-day reports. The reporting requirements are aligned  
361 between 21 CFR 314.80 and 600.80 and submitting a single Fifteen-day report containing the  
362 required information is sufficient (see sections IV.C, V.B.1, and V.B.2 below for further  
363 discussion).

364  
365 Additional information on adverse experience reporting in the drug context can be found at:  
366 [https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/uc](https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082056.htm)  
367 [m082056.htm](https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082056.htm).

368 ***2. Five-day reports (see 21 CFR 803.3, 803.53, and 803.56)***

369 For combination products that contain a device constituent part, the Combination Product  
370 Applicant is required to submit Five-day reports (21 CFR 4.102(b)(1) and 4.102(c)(1)(i)). Five-  
371 day reports are required no later than five work days after the day the Combination Product  
372 Applicant becomes aware either that a reportable event for the combination product “necessitates  
373 remedial action to prevent an unreasonable risk of substantial harm to the public health” or that  
374 we (FDA) “have made a written request for the submission of a [Five-day] report” (21 CFR  
375 803.53). Remedial action includes “any action other than routine maintenance or servicing . . .  
376 where such action is necessary to prevent recurrence of a reportable event” (21 CFR 803.3(v)).

377 For example, if the applicant for a prefilled rescue inhaler approved under an NDA determines  
378 that a reportable adverse event was caused by a design flaw that could cause the inhaler actuator  
379 to fail and the drug to not be delivered (which would pose an unreasonable risk of substantial  
380 harm to the public health), and decides to remove the product from the market until the design  
381 can be corrected, a report would be required within five work days after the day that the  
382 applicant becomes aware that such remedial action is necessary (see 21 CFR 803.53). Likewise,  
383 a Five-day report would be required if the applicant for a drug-coated catheter approved under a  
384 PMA determines that a serious injury caused by the catheter breaking was the result of a  
385 manufacturing problem with the bonding process and decides to remove affected product lots  
386 from the market to prevent an unreasonable risk of substantial harm to the public health. For  
387 both of these examples, the applicant must also report the removal action (see 21 CFR  
388 4.102(b)(1), (c)(1)(iii) and 21 CFR Part 806) and can do so as part of the Five-day report (see  
389 section IV.B.3 below for additional discussion of correction or removal reports).

390 Additional information on Five-day reports can be found at:  
391 <https://www.fda.gov/medicaldevices/safety/reportaproblem/default.htm>.

392

### 3. Malfunction reports (see 21 CFR 803.50 and 803.56)

393 For combination products that contain a device constituent part, the Combination Product  
394 Applicant is required to submit Malfunction reports no later than 30 calendar days after the day  
395 the applicant becomes aware of the reportable malfunction (see 21 CFR 4.102(b)(1),  
396 4.102(c)(1)(ii), 803.50, and 803.56). Malfunction reports are required when the applicant  
397 receives or otherwise becomes aware of information that “reasonably suggests”<sup>15</sup> that the  
398 product has malfunctioned and the product, or a similar product marketed by the applicant,  
399 “would be likely to cause or contribute to a death or serious injury if the malfunction were to  
400 recur” (21 CFR 803.3(o)(2)(ii) and 803.50).<sup>16</sup>

401

402 • **Malfunction.** When used in the combination product context, “malfunction” means the  
403 failure of a device constituent part or the product as a whole to meet its performance  
404 specifications or otherwise perform as intended (see 21 CFR 4.102(a) and 803.3(k)).  
405 Performance specifications include all claims made in the labeling for the device  
406 constituent part or the combination product as a whole (see 21 CFR 4.102(a) and  
407 803.3(k)).

408

409 • **“Caused or contributed”** means that an event “was or may have been attributed to” the  
410 product or that the product “was or may have been a factor” in the event, including events  
411 occurring as a result of: (1) failure, (2) malfunction, (3) improper or inadequate design,  
412 (4) manufacture, (5) labeling, or (6) user error (see 21 CFR 803.3(c)).

413

414 • **Serious injury.** As described in 21 CFR 803.3(w), “serious injury” is “an injury or illness  
415 that: (1) [i]s life-threatening, (2) [r]esults in permanent impairment of a body function or  
416 permanent damage to a body structure, or (3) [n]ecessitates medical or surgical  
417 intervention to preclude permanent impairment of a body function or permanent damage  
418 to a body structure. Permanent means irreversible impairment or damage to a body  
419 structure or function, excluding trivial impairment or damage.”

420

421 **Malfunction reports and Fifteen-day reports.** Of particular note for combination products that  
422 contain a device constituent part and are marketed under an ANDA, NDA, or BLA, a  
423 Malfunction report is required in addition to a Fifteen-day report if an adverse experience that  
424 was both serious and unexpected was caused or contributed to by the malfunction. For example,  
425 a Combination Product Applicant determines that a Fifteen-day report is required after a serious

---

<sup>15</sup> See 21 CFR 803.20(c) regarding what kind of information reasonably suggests an event is or is not reportable.

<sup>16</sup> This draft guidance addresses Malfunction reports in light of current policy and practices of the Center for Devices and Radiological Health (CDRH) regarding malfunction reporting. However, CDRH has issued a Federal Register (FR) notice (<https://www.federalregister.gov/documents/2017/12/26/2017-27650/center-for-devices-and-radiological-health-medical-devices-and-combination-products-voluntary>) describing a proposed voluntary program for summary reporting of malfunctions on a quarterly basis by manufacturers, for some devices. As explained in the FR notice, CDRH, in conjunction with OCP, CBER and CDER, is considering whether combination products should be included within the proposed approach for voluntary summary reporting of malfunctions, and is seeking comments on this issue (comments should be submitted to the docket for CDRH’s FR notice; instructions for submitting comments are provided in the FR notice). If combination products are included in the approach for voluntary summary quarterly reporting of malfunctions, FDA intends to update this guidance accordingly.

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426 and unexpected event related to over-infusion from an NDA-approved co-packaged drug and  
427 infusion set. After submitting the Fifteen-day report, the applicant determines that failure of the  
428 infusion set to meet its specifications could have caused or contributed to the event. In this case,  
429 a Malfunction report must also be submitted (see 21 CFR 803.3(k) and 803.50).

430  
431 A Malfunction report may also be required when a Fifteen-day report is not. For example, the  
432 NDA applicant receives a report that before use, a medical professional noticed that the sterile  
433 barrier for a co-packaged syringe was compromised and discarded the syringe before using it on  
434 a patient. No Fifteen-day report is required because there was no adverse event; however, a  
435 malfunction report would be required because a breach in the sterile barrier, if it recurred, could  
436 result in an infection requiring hospitalization for treatment of the infection.

437  
438 Additional information on Malfunction reports can be found at:  
439 <https://www.fda.gov/medicaldevices/safety/reportaproblem/default.htm>.

440 **4. Follow-up Reports (see 21 CFR 314.80, 600.80, 803.56)**

441 As described in 21 CFR 4.101, the requirements for Fifteen-day, Five-day, and Malfunction  
442 reporting for combination products include requirements for follow-up reports. Follow-up  
443 reporting requirements also apply to death and serious injury reports submitted by Combination  
444 Product Applicants for combination products that receive marketing authorization under a  
445 Device Application (see 21 CFR 4.102(b)(1) and 803.56). Follow-up reports are required when  
446 the ICSR submitter becomes aware of reportable new information related to the event that was  
447 not available at the time of the initial report (see 21 CFR 314.80, 600.80, and 803.56).

448  
449 Submission timelines. A follow-up report must be submitted within 15 calendar days for  
450 Fifteen-day reports (or 30 calendar days for combination products marketed under a Device  
451 Application) and 30 calendar days for Five-day, Malfunction, and death or serious injury reports,  
452 of receipt of the new information (see 21 CFR 314.80, 600.80, and 803.56). For example, if a  
453 Combination Product Applicant for an NDA-approved combination product receives reportable  
454 new information related to a previously submitted Fifteen-day report, the information must be  
455 submitted as a follow-up report within 15 calendar days of receipt of the new information.

456  
457 Use of follow-up reports to submit a different type of ICSR related to an initial ICSR. If a  
458 different type of ICSR must be submitted related to an initial ICSR, rather than separately  
459 submitting the different ICSR and a follow-up report to the initial ICSR regarding the new  
460 information, Combination Product Applicants should use the follow-up report to submit the  
461 different type of ICSR. If the different ICSR type has a shorter timeline than a follow-up to the  
462 initial ICSR, the report must be submitted by that shorter timeline. If the different ICSR type has  
463 a longer timeline than the follow-up report type, the Agency does not intend to object if the  
464 applicant submits the report by that later timeline. See also Section V.B.3 discussing  
465 information to include in follow-up reports.

466  
467 For example, if a Combination Product Applicant for an NDA-approved combination product  
468 submits a Fifteen-day report, and later determines that a Five-day report must be made regarding  
469 the need for remedial action, the Five-day report should be submitted as a follow-up report to the

470 previously submitted Fifteen-day report, and must be submitted within 5 work days after the day  
471 the applicant becomes aware that remedial action is needed. In contrast, if the applicant receives  
472 information that a reportable malfunction also occurred, the Agency does not intend to object if  
473 the applicant submits the malfunction report as a follow-up report to the previously submitted  
474 Fifteen-day report within 30, rather than 15, calendar days after the day the applicant receives the  
475 malfunction information.

#### 476 ***5. Combination Product ICSR Information Included in Periodic Safety Reports***

477 Under the combination product PMSR rule, periodic reporting is required for combination  
478 products marketed under an NDA, ANDA, or BLA. If such a combination product includes a  
479 device constituent part, these periodic reports must include a summary and analysis of the Five-  
480 day and Malfunction reports submitted during the reporting interval for the periodic safety  
481 reports required under 21 CFR 314.80(c)(2) and 600.80(c)(2) (see 21 CFR 4.102(d)(1)). See  
482 section V.B.4 below for additional information on how to submit such information in a periodic  
483 safety report.

484  
485 For combination products marketed under a Device Application, periodic reporting is *not*  
486 required. Additional reporting is required *only* if the FDA notifies the Combination Product  
487 Applicant in writing that the Agency requires additional information. When such reporting is  
488 required for a combination product, which the Agency anticipates will be rare, FDA will specify  
489 what additional safety information is needed (see 21 CFR 4.102(d)(2)).

#### 490 ***6. Combination Product ICSRs for Foreign Events or Experiences***

491 The reporting requirements for foreign events for combination products align with the underlying  
492 regulatory requirements for drugs, devices, and biological products (see 21 CFR 4.102).

493  
494 Fifteen-day reports for combination products must address foreign experiences consistent with  
495 the requirements for drugs and biological products (see 21 CFR 314.80(c)(1) and 600.80(c)(1)).  
496 Combination Product Applicants for combination products that include a drug or biological  
497 product must submit Fifteen-day reports for foreign adverse experiences that are both serious and  
498 unexpected, unless they can confirm that the event did not involve their product (for example,  
499 they can confirm that the event was associated with another manufacturer's product).

500  
501 Likewise, Combination Product Applicants for combination products containing device  
502 constituent parts should submit other ICSRs to FDA for otherwise reportable events for the same  
503 or similar combination product marketed outside of the U.S. by that applicant.<sup>17</sup> For example, if  
504 the Combination Product Applicant for a drug-eluting stent markets such stents in additional  
505 sizes outside the U.S., and those products are otherwise similar<sup>18</sup> to the product marketed in the

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<sup>17</sup> See Guidance for Industry and FDA Staff, *Medical Device Reporting Requirements for Manufacturers*  
(<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm359566.pdf>)

<sup>18</sup> “Similar” means the product has the same basic design and performance characteristics related to safety and effectiveness and the same intended use. See Guidance for Industry and FDA Staff, *Medical Device Reporting Requirements for Manufacturers*  
(<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm359566.pdf>)

506 U.S., then death, serious injuries, and malfunctions that occur with those products, including  
507 sizes not marketed in the U.S., and any such event that necessitates remedial action as described  
508 in 21 CFR 803.53, should still be reported to FDA.

509

510 Combination Product Applicants who have questions about reporting requirements for foreign  
511 events should contact the lead Center or OCP, as needed.

## 512 **B. Other (Non-ICSR) Combination Product PMSR Report Types**

513 Please note that each of the sections below discusses circumstances under which the specified  
514 report type may be required.<sup>19</sup> These discussions are not intended to identify all reports that may  
515 be required in relation to the events described, and what reports may be required in events  
516 similar to those described may differ, depending on the specific circumstances. As indicated  
517 below, in some cases, multiple report types may be required and it may be possible to satisfy  
518 multiple reporting requirements in the same submission as discussed more fully in section V.A.3  
519 below.

### 520 **1. Field alert reports (see 21 CFR 314.81)**

521 For combination products that contain a drug constituent part, the Combination Product  
522 Applicant is required to submit field alert reports (FARs) (see 21 CFR 4.102(b)(2) and  
523 4.102(c)(2)(i)). FARs are required within three working days of receipt of information for the  
524 following issues: “any incident that causes the [product] or its labeling to be mistaken for, or  
525 applied to, another article,” or “concerning any bacteriological contamination, or any significant  
526 chemical, physical, or other change or deterioration in the distributed [product] or any failure of  
527 one or more distributed batches of the [product] to meet the specification established for it in the  
528 application” (see 21 CFR 314.81).

529

530 For combination products, a FAR is submitted for any of the issues described above that could  
531 have resulted from any of the constituent parts of the combination product or the manufacturing  
532 process for the combination product. For example, bacteriological contamination of a prefilled  
533 syringe could be the result of contamination during the manufacturing of the drug prior to filling,  
534 contamination of the syringe before it is filled, or contamination that occurs during the filling  
535 process. In any case, if the product is contaminated, a FAR must be submitted. Likewise, if the  
536 coating on a drug-eluting stent does not meet specifications because of impurities introduced  
537 during coating formulation or because of impurities on the metal stent, a FAR must be submitted.

538

539 A FAR must be submitted even if the issue resulted from material supplied to the applicant by  
540 another party. For example, if a Combination Product Applicant whose combination product is  
541 approved under a Device Application detects bacteriological contamination and determines that  
542 the problem is due to a supplier’s drug product, the Combination Product Applicant must submit

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For example, if the device constituent part of a combination product marketed outside the U.S. by the Combination Product Applicant is the same or similar to a device constituent part of a combination product marketed in the U.S., then reportable malfunctions for that foreign product should be reported.

<sup>19</sup> Although not specifically discussed in this section, additional information may be required to be submitted after submission of a non-ICSR report (see, e.g., 21 CFR 806.10(c)(13) and (d)).

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543 a FAR and should also communicate with the drug product supplier to enable any additional  
544 actions and reporting by the drug product supplier as appropriate.

545  
546 Additional information on FARs can be found at:  
547 [https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm52973](https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm529734.htm)  
548 [4.htm](https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm529734.htm) and  
549 [https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceinformation/ucm529](https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceinformation/ucm529890.htm)  
550 [890.htm](https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceinformation/ucm529890.htm).

551 **2. Biological product deviation reports (BPDRs) (see 21 CFR 600.14 and 606.171)**

552 BPDRs are required for combination products that contain a biological product constituent part  
553 (see 21 CFR 4.102(b)(3) and 4.102(c)(3)(i)). BPDRs are required “for any event, and  
554 information relevant to the event, associated with the manufacturing, to include testing,  
555 processing, packing, labeling, or storage, or with the holding or distribution,” of a product, if that  
556 event, either:<sup>20, 21</sup>

- 557
- 558 • Represents a deviation from current good manufacturing practice, applicable regulations,  
559 applicable standards, or established specifications that may affect the safety, purity, or  
560 potency of that product; or
- 561 • Represents an unexpected or unforeseeable event that may affect the safety, purity, or  
562 potency of that product; and
  - 563 ○ Occurs in the applicant’s facility or another facility under contract with the  
564 applicant; and
  - 565 ○ Involves a distributed product

566  
567 (21 CFR 600.14 and 606.171).

568  
569 BPDRs should be submitted as soon as possible and must be submitted no later than 45 calendar  
570 days from the day of acquiring information “reasonably suggesting” that a reportable event has  
571 occurred (21 CFR 600.14 and 606.171).

572  
573 For combination products, BPDRs can be related to the non-biological product constituent  
574 part(s). For example, a BPDR would be required if a prefilled syringe of a vaccine incorporates  
575 syringe components that do not meet required specifications for such materials and that deviation  
576 may affect the safety, purity, or potency of the product. BPDRs may also be required when there  
577 are manufacturing process deviations for a combination product. For example, if there is a  
578 manufacturing deviation that could impact the purity of a recombinant bone morphogenetic

---

<sup>20</sup> See also Guidance for Industry, [Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM163923.pdf) (<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM163923.pdf>).

<sup>21</sup> See also Guidance for Industry, [Biological Product Deviation Reporting for Blood and Plasma Establishments](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM062918.pdf) (<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM062918.pdf>).

579 protein in a distributed PMA-approved bone graft combination product, that deviation must be  
580 reported in a BPDR.

581 **3. Correction or removal reports (see 21 CFR 806.10)**

582 For combination products that contain a device constituent part, the Combination Product  
583 Applicant is required to submit reports of corrections and removals within 10 working days of  
584 initiating a correction or removal, to “reduce a risk to health posed by the [product]” or “remedy  
585 a violation of the [FD&C Act] caused by the [product] which may present a risk to health” (21  
586 CFR 4.102(b)(1), (c)(1)(iii), and 806.10).

587  
588 For purposes of the combination product PMSR final rule and this guidance, “correction” means  
589 any “repair, modification, adjustment, relabeling, destruction, or inspection (including patient  
590 monitoring) of a [product] without its physical removal from its point of use to some other  
591 location” (21 CFR 806.2(d)). “Removal” means “the physical removal of a [product] from its  
592 point of use to some other location for repair, modification, adjustment, relabeling, destruction,  
593 or inspection” (21 CFR 806.2(j)). Examples of actions reportable under this requirement  
594 include:

- 595
- 596 • Removing a combination product from the market because of a manufacturing or design  
597 issue that poses a risk to health
  - 598
  - 599 • Removing a product from the market because the product contains contaminants that  
600 could result in infection or adverse reactions in patients
  - 601

602 The Combination Product Applicant must submit a written report to FDA of any reportable  
603 correction or removal of the combination product, unless the information about the correction or  
604 removal has already been provided through an ICSR required for the combination product, in  
605 which case a separate correction or removal report is not required (see 21 CFR 4.102(b) and (c),  
606 and 21 CFR 806.10).

607 **C. Streamlining Reporting**

608 Under 21 CFR 4.102(b) and (c), a Combination Product Applicant may submit a single report to  
609 comply with more than one reporting requirement if:

- 610
- 611 • The reports can be submitted in the same manner, *and*
  - 612
  - 613 • The combined report satisfies all applicable reporting requirements, including all  
614 submission timelines.
  - 615

616 “In the same manner” means that a report is submitted in the same way (e.g., electronic, paper  
617 submission) and to the same recipient group within FDA (e.g., via a common electronic  
618 gateway).

619

620 As explained more fully in section V.A.3 below, such streamlining is available for ICSRs and  
621 correction and removal reports because a Combination Product Applicant is required to submit  
622 all ICSRs for its combination product in the same manner and can provide correction and  
623 removal information in this manner as well.

#### 624 **D. Information Sharing Between Constituent Part Applicants**

625 Under 21 CFR 4.103, Constituent Part Applicants must share information with the other  
626 Constituent Part Applicant(s) for the same combination product regarding an event associated  
627 with the combination product that involves a death or serious injury as described in 21 CFR  
628 803.3, or an adverse experience as described in 21 CFR 314.80(a) and 600.80(a).

629  
630 This requirement applies regardless of whether the event is expected or unexpected (see section  
631 IV.A.1). However, if a Constituent Part Applicant receives information regarding an event that  
632 does not involve a death, serious injury or other adverse experience, the Constituent Part  
633 Applicant has no duty under the rule to share the information with the other Constituent Part  
634 Applicant(s) for the combination product.

635  
636 The definition of “adverse experience” is broad and encompasses death and serious injuries;  
637 hence, the Constituent Part Applicant does not need to evaluate an event involving an adverse  
638 experience further (e.g., with regard to seriousness or causality) prior to sharing the information.  
639

640 To comply with section 4.103, the Constituent Part Applicant need only share the initial  
641 information it receives regarding the event and may do so by merely forwarding the information  
642 to the other Constituent Part Applicant. There is no requirement to develop a report or analysis  
643 of the event for the other Constituent Part Applicant.

644  
645 For example:

- 646  
647 • A cross-labeled combination product is composed of a drug constituent part being  
648 marketed under an NDA held by one Constituent Part Applicant, and a device constituent  
649 part being marketed under a Device Application held by the other Constituent Part  
650 Applicant. The drug Constituent Part Applicant receives information that during use of  
651 the combination product, a patient received a severe skin burn. The drug Constituent Part  
652 Applicant must forward to the device Constituent Part Applicant that initial information  
653 received by the drug Constituent Part Applicant regarding the event.  
654
- 655 • A cross-labeled combination product is composed of a delivery device constituent part  
656 marketed under a Device Application held by one Constituent Part Applicant and of a  
657 drug constituent part marketed under an NDA held by the other Constituent Part  
658 Applicant. The device Constituent Part Applicant receives information on a device  
659 constituent part malfunction that did not occur during patient use and did not result in a  
660 death, serious injury, or other adverse experience. The device Constituent Part Applicant  
661 must report the event to FDA as appropriate under 21 CFR Part 803 reporting  
662 obligations, but is not required to share the information with the drug Constituent Part  
663 Applicant because no serious injury, death or other adverse experience occurred.



664  
665 In addition to sharing information with each other, Constituent Part Applicants must report  
666 events to FDA as required by the PMSR regulations applicable to their respective constituent  
667 part (see 21 CFR 4.102(b)). Such reports to FDA should address how the event is related to the  
668 constituent part and the combination product as a whole.

669  
670 As reflected in footnote 2 above, if you are uncertain of whether your product is a constituent  
671 part of a combination product, you may contact OCP. However, we note that the purpose of 21  
672 CFR 4.103 is to ensure sharing of adverse event information between entities who are  
673 collaborating to market products intended for use with one another, to help ensure timely,  
674 complete reporting to FDA. Accordingly, we encourage such applicants to share such  
675 information with one another regardless of whether the products necessarily comprise a  
676 combination product.

## 677 **E. Recordkeeping Requirements**

678 21 CFR 4.105 addresses PMSR recordkeeping requirements for Constituent Part Applicants and  
679 Combination Product Applicants as follows.

680  
681 Constituent Part Applicants. A Constituent Part Applicant must retain PMSR records for the  
682 time-periods stipulated in the regulations applicable to its type of constituent part (see 21 CFR  
683 4.102(b) and 4.105(a)(1)). In addition, Constituent Part Applicants must retain records of the  
684 information they provide to the other Constituent Part Applicant(s) in accordance with 21 CFR  
685 4.103, for the longest period required for any records under the PMSR requirements applicable to  
686 the Constituent Part Applicant who shared the information (21 CFR 4.105(a)(2)).

687  
688 For example: PharmaCo holds an NDA for a drug constituent part of a combination product, and  
689 MedCo holds a PMA for the device constituent part.

690  
691 PharmaCo receives a report of an adverse experience and shares the information with MedCo.  
692 PharmaCo must retain a record of the information it shared with MedCo for 10 years from the  
693 date PharmaCo received the information because the only PMSR requirement with a  
694 recordkeeping period applicable to PharmaCo is 10 years for adverse drug experiences (see 21  
695 CFR 314.80(j)). MedCo must retain records relating to the event for the time-period required  
696 under the device PMSR regulations applicable to MedCo with regard to the event. For example,  
697 for malfunction or serious injury or death reporting, MedCo would be required to keep records  
698 for the longer of 2 years from the date of the event or a period equivalent to the expected life of  
699 the device, whichever is greater, in accordance with the recordkeeping requirements under 21  
700 CFR Part 803.

701  
702 However, if MedCo were to receive information about another adverse experience associated  
703 with administration of the combination product, it would have to share that initial information  
704 with PharmaCo and must retain records of sharing the information for the longest of the record  
705 retention periods applicable to MedCo for the device constituent part: either 2 years from the  
706 date of the event (see 21 CFR 803.18(c)) or 2 years beyond the expected life of the device (see  
707 21 CFR 806.20 requirements for corrections and removals), because Part 806 recordkeeping

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708 requirements apply to MedCo in addition to the Part 803 requirements. PharmaCo would again  
709 have to retain this information for the 10-year period applicable to it for all adverse experiences  
710 for the drug constituent part.

711  
712 Section 4.103(b) states that the records kept of the information a Constituent Part Applicant  
713 shares with another Constituent Part Applicant must include: a copy of the information provided  
714 to the other Constituent Part Applicant(s); the date the information was received by the  
715 Constituent Part Applicant who shared the information; the date the information was shared; and  
716 the name and address of the other Constituent Part Applicant(s) with whom the information was  
717 shared.

718  
719 Combination Product Applicants. Combination Product Applicants must retain records for the  
720 longest time-period required for records under all PMSR requirements applicable to the  
721 combination product (see 21 CFR 4.105(b)). For example, for a Combination Product Applicant  
722 for a drug-device combination product, the required recordkeeping period for PSMR records is  
723 the longest of the following periods:

- 724
- 725 • 10 years, which is the recordkeeping period for all adverse experiences known to the  
726 applicant (see 21 CFR 314.80(j))
  - 727 • 2 years from the date of the event or a period of time equivalent to the expected life of the  
728 product, whichever is greater, which is the recordkeeping period for records under 21  
729 CFR Part 803 (see 21 CFR 803.18)
  - 730 • 2 years beyond the expected life of the product, which is the recordkeeping period for  
731 records under 21 CFR Part 806 (see 21 CFR 806.20).

732  
733 Therefore, for a drug-device combination product, the Combination Product Applicant is subject  
734 to a recordkeeping period of 10 years unless the combination product has an expected life of  
735 more than 8 years, in which case, the records must be kept for two years beyond the expected life  
736 of the product. If, for example, an implantable drug-device combination product has an expected  
737 life of 3 years, the longest recordkeeping requirement that would apply would be 10 years.  
738 Conversely, if that combination product had an expected life of 9 years, the longest  
739 recordkeeping requirement that would apply would be the expected life plus two years (equaling  
740 11 years in this case).

## 741 **V. Process Considerations for Combination Product Applicants**

742 The sections below provide guidance to Combination Product Applicants on where, how, and  
743 when to submit PMSR reports to FDA. Because it is expected that Constituent Part Applicants  
744 are already familiar with the reporting processes applicable to their constituent part, the  
745 processes for submitting PMSR reports for Constituent Part Applicants are not specifically  
746 discussed in these sections (but see 21 CFR 4.104(a)).

747 **A. How to Submit Combination Product PMSR Information to FDA**

748 **1. What timelines do I follow for submitting the reports?**

749 Combination Product Applicants follow the timelines associated with the report type with the  
 750 exception that for combination products that received marketing authorization under a Device  
 751 Application, Fifteen-day reports under 21 CFR 314.80 or 600.80 can be submitted within 30  
 752 calendar days, rather than within 15 days (see 21 CFR 4.102(c)(2)(ii) and (c)(3)(ii)). The  
 753 reporting timelines are summarized below.

754 **Table 1. Timelines for Various Combination Product PMSR Requirements**

<b>Report Type</b>	<b>Timeline for Reporting</b>
Fifteen-day Reports	No later than <u>15 calendar days</u> from initial receipt of the information by the applicant (see 21 CFR 314.80(c) and 600.80(c))  EXCEPTION for combination products that received marketing authorization under a Device Application: No later than <u>30 calendar days</u> from initial receipt of information by the applicant (see 21 CFR 4.102(c))
Follow-ups to Fifteen-day Reports	Within <u>15 calendar days</u> of receipt of new information (see 21 CFR 314.80(c) and 600.80(c)).  EXCEPTION for combination products that received marketing authorization under a Device Application: No later than <u>30 calendar days</u> from initial receipt of the information by the applicant (see 21 CFR 4.102(c)).
Five-day Reports	No later than <u>5 work days</u> after the day that you become aware of the event (see 21 CFR 803.53)
Death/Serious Injury/Malfunction Reports	No later than <u>30 calendar days</u> after the day that you become aware of the event (see 21 CFR 803.50)
Supplements/ Follow-ups to Five-day/Death/Serious Injury/Malfunction Report	Within <u>30 calendar days</u> of the day that you receive the information (see 21 CFR 803.56)
Field Alert Reports	Within <u>3 working days</u> of receipt of the information by the applicant (see 21 CFR 314.81(b)(1))
Biological Product Deviation Reports	As soon as possible but not to exceed <u>45 calendar days</u> from the date of acquiring information reasonably suggesting that a reportable event has occurred (see 21 CFR 600.14(c) and 606.171(c))
Correction and Removal Reports	Within <u>10 working days</u> of initiating correction or removal (see 21 CFR 806.10(b))

756  
 757 Note that a follow-up report should be used to submit an additional ICSR type relating to the  
 758 same event (e.g., a malfunction report concerning an event for which the applicant has already

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759 submitted a Fifteen-day report). If the additional report type has a shorter timeline than the  
760 follow-up report type, the report must be submitted by that shorter timeline. If a follow-up report  
761 is used to submit an additional report type and the additional report type has a longer timeline,  
762 the Agency does not intend to object if the applicant submits the report by that later timeline (see  
763 section IV.A.4 above).

764 **2. Where/how do I submit reports?**

765 ICSRs (including Follow-up Reports). To comply with the requirements in 21 CFR 4.104(b),  
766 Combination Product Applicants must submit ICSRs in the manner stipulated in the  
767 requirements associated with the application type, and should follow relevant policies and  
768 procedures of the lead Center.

769 Accordingly, for:

- 770
- 771
  - 772 • A Device Application combination product, submit all ICSRs (including Fifteen-  
773 day reports) in accordance with 21 CFR 803.12(a) and associated guidance  
774
  - 775 • An NDA or ANDA combination product, submit all ICSRs (including Five-day  
776 reports and Malfunction reports if the combination product includes a device  
777 constituent part) in accordance with 21 CFR 314.80(g) and associated guidance  
778
  - 779 • A BLA combination product, submit all ICSRs (including Five-day reports and  
780 Malfunction reports if the combination product includes a device constituent part)  
781 in accordance with 21 CFR 600.80(h) and associated guidance  
782

783 As with initial reports, submit follow-up reports to ICSRs in the manner specified in the  
784 regulations and policies associated with the application type for the combination product. For  
785 example, if the combination product received marketing authorization under a Device  
786 Application, submit follow-up reports to Fifteen-day reports in accordance with 21 CFR  
787 803.12(a) and implementation specifications for CDRH eMDR  
788 ([https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/  
789 ReportingAdverseEvents/ucm127951.htm](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127951.htm)).

790

791 Other (Non-ICSR) Report Types. For report types other than ICSRs (i.e., FARs, BPDRs, and  
792 correction and removal reports), submit reports in accordance with the regulations and policies  
793 associated with the report type.

794

795 For additional information on reporting, see:

- 796
- 797 • ICSRs:
    - 798 ○ Draft Guidance for Industry, *Providing Submissions in Electronic Format —*  
799 *Postmarketing Safety Reports*, which, when final, will represent FDA’s current  
800 thinking on this topic  
801 (<https://www.fda.gov/downloads/drugs/guidances/ucm072369.pdf>).

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- 802           ○ Implementation specifications for CDRH eMDR, found at:  
803           [https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Postmarket](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127951.htm)  
804           [Requirements/ReportingAdverseEvents/ucm127951.htm](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127951.htm)  
805           ○ Technical specifications for CBER/CDER electronic ICSRs, contained in  
806           *Specifications for Preparing and Submitting Electronic ICSRs and ICSR*  
807           *Attachments*  
808           ([https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance](https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm115894.htm)  
809           [/adversedrugeffects/ucm115894.htm](https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm115894.htm))  
810  
811           ● Field Alert Reports:  
812           [https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/uc](https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm529729.htm)  
813           [m529729.htm](https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm529729.htm)  
814           [https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformati](https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ucm529890.htm)  
815           [on/ucm529890.htm](https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ucm529890.htm)  
816  
817           ● Recalls, Corrections and Removals:  
818           [https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequiremen](https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/recallscorrectionsandremovals/default.htm)  
819           [ts/recallscorrectionsandremovals/default.htm](https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/recallscorrectionsandremovals/default.htm)  
820  
821           ● Biological Product Deviation Reports:  
822           [https://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/biological](https://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/biologicalproductdeviations/default.htm)  
823           [productdeviations/default.htm](https://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/biologicalproductdeviations/default.htm)

824           **3. *How can I streamline reports for the same event?***

825           Combination Product Applicants may submit a single ICSR rather than separate reports to  
826           comply with more than one reporting requirement that is appropriately made through an ICSR  
827           (see section IV.C above). For example:

- 828  
829           ● A Combination Product Applicant who holds an approved NDA for a drug-device  
830           combination product must submit both a Fifteen-day (see 21 CFR 314.80) and  
831           Malfunction (see 21 CFR 803.50) report for an event that triggers both duties. That  
832           applicant could satisfy both requirements by submitting a single report within 15 days  
833           that includes all of the information that would be required in both types of reports for the  
834           event.  
835  
836           ● A Combination Product Applicant who holds an approved PMA for a device-biological  
837           product combination product must submit a death/serious injury report (see 21 CFR Part  
838           803), Fifteen-day (see 21 CFR 600.80) and Five-day (see 21 CFR 803.3 and 803.53)  
839           report. The applicant can satisfy all of these requirements by submitting a single report  
840           that contains all required information and is submitted no more than 30 calendar days  
841           after the adverse event information was originally received and no more than 5 work days  
842           after determining that remedial action was needed.  
843

844           See section V.B below for additional information on what to include in reports.

845 **B. What Information to Include in Combination Product PMSR**  
846 **Reports**<sup>22</sup>

847 **1. General content when submitting combination product PMSR reports**

848 PMSR reports for combination products must contain all information required for the report  
849 under the applicable regulations, including relevant information on the entire product (including  
850 each constituent part). Also, in situations where the Combination Product Applicant submits  
851 multiple types of reports for the same event or product problem, the reports should include cross-  
852 references to each other.

853 **2. Additional information to include in combination product ICSRs**

854 This section identifies the types of information that Combination Product Applicants should  
855 include in ICSRs if not already required under the applicable regulations for the report type.  
856 Please see technical specifications and instructions for the various ICSR reporting mechanisms  
857 for specific details on how to complete and submit reports.<sup>23</sup>

858 Include the following information in combination product ICSRs (except for combination  
859 products that include a vaccine and that received marketing authorization under a BLA),<sup>24</sup>  
860 regardless of which constituent part was implicated in the event. For example, even if an event  
861 requiring a Fifteen-day report appears to have no relationship to the device constituent part,  
862 include the information on what device constituent part is contained in the combination product.  
863 (See Appendix 4 for which fields address which elements.)

- 864
- 865 • Combination Product Identifier. Indicate that the report is for a combination product.
  - 866
  - 867 • Report Type(s). Identify the type of report. If one report is being made to cover multiple  
868 reporting requirements, each report type should be identified (e.g., if the report covers  
869 both Fifteen-day and Malfunction reporting requirements, the appropriate identifier  
870 should be included for each report type).
  - 871

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<sup>22</sup> As explained in note 16, *supra*, if combination products are included in the approach for summary quarterly reporting of malfunctions, FDA intends to update this guidance accordingly.

<sup>23</sup> Although FDA has identified in this section information that Combination Product Applicants should include in ICSRs, there are additional data elements available for Combination Product Applicants in the reporting systems. Combination Product Applicants are encouraged to submit additional elements, when available. For additional information, see FDA Adverse Events Reporting System (FAERS) Electronic Submissions Webpage (<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm115894.htm>) and eMDR – Electronic Medical Device Reporting Webpage (<https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/reportingadverseevents/emdr%E2%80%93electronicmedicaldevicereporting/default.htm>).

<sup>24</sup> Similar updates to the Vaccine Adverse Event Reporting System (VAERS) to address combination products are being considered. FDA is evaluating what additional data elements to include in the VAERS system and welcomes comments from combination product vaccine reporters on this topic.

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- 899
- 900
- 901
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- 903
- 904
- 905
- 906
- 907
- Patient Identifier. Provide a patient identifier. If there was no patient involved in the event (e.g., if only a malfunction occurred), enter “None.”
  - Reporter Identifier. Identifier for the individual that provided the initial report to the Combination Product Applicant.
  - Suspect Medical Device. Include at least one of the following for the device constituent part: the product code (procode), the device common name, and/or the brand name. FDA maintains a searchable online [procode database](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) (that includes both procodes and device common names) (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>). Combination Product Applicants should select the procode that most closely aligns with the device constituent part<sup>25</sup> (include regardless of whether or not you believe the device constituent part was implicated in the event.)
  - Suspect Drug or Biological Product(s). Enter the known product attributes for the drug or biological product constituent part (e.g., trade name, active ingredient(s), dosage form, strength). Combination Product Applicants should include drug or biological product attributes (include regardless of whether or not you believe the drug or biological product constituent part was implicated in the event). For NDA/ANDA/BLA approved products, include the application number.
  - Adverse Event Coding.
    - For Device Application combination products, enter Patient Problem Code. Identify at least one patient problem code. FDA maintains an [online list](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAverseEventCodes/ucm584205.htm) of patient problem codes or the submitter may enter descriptive term (<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAverseEventCodes/ucm584205.htm>).
    - For NDA/ANDA/BLA combination products, enter Reaction/Event Coding. FDA encourages the use of MedDRA (Medical Dictionary for Regulatory Activities) terms. For a malfunction-only report, enter a MedDRA code associated with a relevant product quality issue<sup>26</sup> or “No adverse event.”
  - Device Problem Code. Identify at least one device problem code. FDA maintains an [online list](#) of device problem codes

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<sup>25</sup> Some examples of procodes for delivery devices that often comprise constituent parts of NDA/ANDA/BLA combination products include: Syringe, Piston (procode FMF), Injector, Pen (procode NSC), Nebulizer (Direct Patient Interface) (procode CAF), Set, Administration, Intravascular (procode FPA), Tubing, Fluid Delivery (procode FPK), and IV Container (procode KPE). If a Combination Product Applicant is unable to identify an appropriate procode, they may contact CDRH’s Division of Industry and Consumer Education (DICE), ([DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)) for assistance, as well as OCP as needed.

<sup>26</sup> For additional information on use of MedDRA coding, see *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm153588.pdf>).

908 <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm>). If there is  
909 no device problem associated with the ICSR, enter the device code for “No Known  
910 Device Problem” for this field.  
911

- 912
- 913 • **Cross-Reference to Other Reports.** As indicated in section V.B.1 above, in addition to  
914 the above, if an ICSR is related to other reports made to FDA (e.g., if a FAR is also  
915 required), the Combination Product Applicant should provide cross-reference to such  
916 other reports in the narrative discussion.

### 917 **3. Information to include in Follow-up ICSRs**

918 In determining what information to include in follow-up ICSRs, follow applicable regulations,  
919 policies, and procedures of the application type for the combination product.<sup>27</sup> For Device  
920 Application combination products, include in follow-up reports only the new, changed or  
921 corrected information (see 21 CFR 803.56(c)), whereas for NDA/ANDA/BLA combination  
922 products, include in follow-up reports relevant information from the initial report combined with  
923 the new information.<sup>28</sup> See also Section IV.A.4 for additional discussion on use of follow-up  
924 reports to submit a different type of ICSR related to an initial ICSR.

### 925 **4. Additional information to include in periodic safety reports for** 926 **ANDA/NDA/BLA combination products that include a device**

927 When NDA/ANDA/BLA Combination Product Applicants submit a periodic adverse drug  
928 experience report (PADER) or periodic adverse experience report (PAER), information from any  
929 initial and follow-up Five-day and Malfunction reports, in addition to any Fifteen-day reports,  
930 submitted during the reporting interval must be addressed in the section that contains summary  
931 and analysis of reports submitted during the interval (see 21 CFR 4.102(d)(1), 314.80(c)(2)(ii)  
932 and 600.80(c)(2)(ii)). Similarly, when a Combination Product Applicant is granted a waiver to  
933 substitute the *International Council for Harmonisation (ICH) E2C(R1) Periodic Safety Update*  
934 *Report (PSUR)* or *ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* for the  
935 PADER or PAER, the applicant must include information about Five-day and Malfunction  
936 reports as well as Fifteen-day reports (see 21 CFR 4.102(d)(1)). Such information may be  
937 included in the body of the report or as an appendix to the PSUR or PBRER.<sup>29</sup>  
938

---

<sup>27</sup> Submitting follow-up ICSRs consistent with the applicable regulations, policies, and procedures associated with the application type complies with 21 CFR 4.104(b). For example, for drug-led combination products, the Center for Drug Evaluation and Research’s (CDER) electronic reporting system accepts follow-up reports to ICSRs based on the requirements in 21 CFR Part 314 and relevant CDER policies and procedures.

<sup>28</sup> See Draft Guidance for Industry, *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines* (<https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm092257.pdf>) which, when final, will represent the FDA’s current thinking on this topic.

<sup>29</sup> For more information about PBRER, see Guidance for Industry, *Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)* (<https://www.fda.gov/downloads/drugs/guidances/ucm346564.pdf>).



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939 Any questions on periodic reporting or additional required reporting for a combination product  
940 should be directed to the lead Center for the combination product or OCP as needed.

941 **5. *Additional information to include in non-ICSR combination product reports***  
942 ***(correction and removal report, FAR, or BPDR)***

943 In addition to the other information appropriately included in the type of report,

944

945 When submitting a correction and removal report:

946

- 947 • Identify the product as a combination product and provide a description of the  
948 combination product, including its constituent parts. If the product includes a device  
949 constituent part, include the device product code and the device common name.
- 950 • Include the Combination Product Applicant name, address, telephone number, and  
951 contact person (if not otherwise required to be included in the correction and removal  
952 report)
- 953 • Cross-reference to the identifier(s) for any related PMSR reports (i.e., related ICSRs,  
954 FARs, BPDRs, if applicable)

955

956 When submitting a FAR:

957

- 958 • Identify the product as a combination product and provide a description of the  
959 combination product, including its constituent parts, and how these constituent parts are  
960 or may be involved in the quality defect. If the product includes a device constituent part,  
961 include the device product code and the device common name.
- 962 • Cross-reference to the identifier(s) for any related PMSR reports (i.e., related ICSRs,  
963 correction and removal reports, BPDRs, if applicable)

964

965 When submitting a BPDR:

966

- 967 • Identify the product as a combination product and provide a description of the  
968 combination product, including its constituent parts. If the product includes a device  
969 constituent part, include the device product code and the device common name.
- 970 • Cross-reference to the identifier(s) for any related PMSR reports (i.e., related ICSRs,  
971 correction and removal reports, FARs, if applicable)

972 **VI. Examples**

973 The hypothetical examples in this section illustrate PMSR considerations for Combination  
974 Product Applicants under 21 CFR Part 4. This section is not intended to reflect a complete  
975 analysis of the reporting obligations that may apply, and specific products and events may raise  
976 distinct issues that are not taken into account in the hypothetical scenarios presented below. If  
977 manufacturers have specific questions, FDA recommends that they contact the lead Center for  
978 the product or OCP, as needed, for assistance.

979 **A. Drug application combination product**

980 **1. Product Description and Scenario**

981 A Combination Product Applicant holds an NDA for a combination product consisting of a  
982 sterile syringe pre-filled with an injectable drug. The applicant receives a report that a user was  
983 unable to pull back the syringe plunger rod initially, and when he managed finally to pull the  
984 plunger back, the entire plunger came out, and the product sprayed into his eyes, causing  
985 temporary blindness and requiring medical intervention to prevent serious damage to his  
986 eyes. The Combination Product Applicant reviews the combination product labeling and notes  
987 that potential blindness is not an expected adverse event discussed in the labeling.

988 **2. Initial ICSR Reporting**

989 The Combination Product Applicant assesses its ICSR reporting obligations for the event (see  
990 Chart 2.1 in Appendix 2):

- 991
- 992 • Was the event an adverse experience that was both serious and unexpected?  
993  
994 YES. The event was both serious and unexpected (was not included in the product  
995 labeling). A Fifteen-day report is required.  
996
  - 997 • Does the product contain a device constituent part? YES.  
998
  - 999 • Did the report reasonably suggest that the product malfunctioned and that the product or a  
1000 similar product marketed by the applicant would be likely to cause or contribute to a  
1001 death or serious injury if the malfunction were to recur?  
1002  
1003 YES. The report indicated that the device did not perform as intended, which resulted in  
1004 temporary blindness. A Malfunction report is required.  
1005
  - 1006 • Did the event necessitate remedial action to prevent an unreasonable risk of substantial  
1007 harm to the public health?  
1008  
1009 NO. At the time of the initial report, no information is available to the Combination  
1010 Product Applicant to indicate that a remedial action is necessary to prevent an  
1011 unreasonable risk of substantial harm. A Five-day report is not required at this time.  
1012

1013 The reporting timeline for the Fifteen-day report is 15 calendar days and for the Malfunction  
1014 report, it is 30 calendar days. The Combination Product Applicant provides a report that  
1015 includes the relevant information for a Fifteen-day and Malfunction report, including the  
1016 information identified in sections V.B.1 and V.B.2 above, and submits the report within 15  
1017 calendar days and thereby, complies with both of these combination product PMSR  
1018 requirements.

1019 **3. Reporting based on Additional Information Received**

1020 The Combination Product Applicant continues to investigate the event, and determines that the  
1021 supplier of the syringe made changes to the material of the plunger without notifying the  
1022 Combination Product Applicant and that the new material alters the force needed to pull the  
1023 plunger during use.

1024 ICSR Considerations. Based on this new information, the Combination Product Applicant  
1025 reassesses the event and determines that a remedial action, specifically the removal of lots of the  
1026 combination product that include the syringes with the new material, is necessary to prevent an  
1027 unreasonable risk of substantial harm. Within five working days of making this determination,  
1028 the Combination Product Applicant submits a Five-day report, which is also a follow-up report  
1029 to the initial ICSR.

1030  
1031 Non-ICSR PMSR Considerations. The Combination Product Applicant determines that the  
1032 change is inconsistent with a specification established in the application for the combination  
1033 product and submits a FAR as required within three working days of receiving the information  
1034 that the combination product was not meeting the specification established in its application.

1035  
1036 Because the Combination Product Applicant did not initiate the removal until after submitting  
1037 the Five-day report, it submits a separate correction and removal report that includes the relevant  
1038 information, including the information identified in section V.B.5 above within 10 working days  
1039 of initiating the product removal.

1040  
1041 **4. Additional Considerations for this Scenario**

1042 Had the Combination Product Applicant made the determination that a removal was necessary to  
1043 prevent an unreasonable risk of substantial harm to the public health and initiated the removal  
1044 early enough, it could have submitted a single report to satisfy the Five-day, correction or  
1045 removal, Malfunction, and Fifteen-day reporting requirements by the earliest of their four  
1046 timelines.

1047  
1048 If the initial event had been expected, reporting would still have been required for the  
1049 malfunction but there would have been no requirement to submit a Fifteen-day report.

1050  
1051 Regardless of what PMSR reports have been submitted to FDA for the combination product,  
1052 subsequent PMSR reports must be submitted to FDA consistent with the combination product  
1053 PMSR final rule. For example, in this scenario, after a Five-day report is submitted, other  
1054 reported adverse events associated with that product problem must continue to be assessed and,  
1055 if required, reported as ICSRs.

1056 **B. Device Application combination product**

1057 **1. Product Description and Scenario**

1058 A Combination Product Applicant holds a PMA for a drug-eluting stent. The applicant receives  
1059 a report that a patient experienced a serious infection after the stent was inserted. Treatment and

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1060 extended hospitalization of the patient was required. The severity of the event exceeds any of  
1061 the warnings on the product labeling.

1062  
1063 The Combination Product Applicant is not able to recover the product that was involved in the  
1064 adverse event, but reviews the production records and finds no anomalies related to any of the in-  
1065 process or finished testing performed on the related product lot.

1066 **2. Initial ICSR Reporting**

1067 The Combination Product Applicant assesses its ICSR reporting obligations for the event (see  
1068 Chart 2.2 in Appendix 2):

1069  
1070 • Was the event an adverse experience that was both serious and unexpected?  
1071  
1072 YES. The serious infection was a serious adverse experience that was unexpected  
1073 because the severity of the event exceeds any of the warnings on the product labeling. A  
1074 Fifteen-day report (made within 30 calendar days) is required.

1075  
1076 • Is the event a reportable death or serious injury?  
1077  
1078 YES. Medical intervention was required to address potentially life-threatening risk to the  
1079 patient after the event. A serious injury report is required.

1080  
1081 • Did the event necessitate remedial action to prevent an unreasonable risk of substantial  
1082 harm to the public health?  
1083  
1084 NO. Review of the production records showed no anomalies in the manufacturing  
1085 process or lot for the product. No other information available to the applicant indicates  
1086 that a remedial action is necessary at this time. No Five-day report is required.

1087  
1088 The reporting timeline for both the Fifteen-day and serious injury reports is 30 calendar days.  
1089 The Combination Product Applicant submits a report within 30 calendar days that includes the  
1090 relevant information for a Fifteen-day and serious injury report, including the information  
1091 identified in sections V.B.1 and V.B.2 above, and thereby, complies with these combination  
1092 product PMSR requirements.

1093 **3. Reporting based on Additional Information Received**

1094 The Combination Product Applicant receives multiple, similar serious infection event reports for  
1095 other patients for the same type of drug-eluting stent. The Combination Product Applicant  
1096 performs additional investigations and determines that the drug coating had contaminants. These  
1097 contaminants are traced to production equipment used to apply the drug coating.

1098  
1099 ICSR Considerations. The applicant determines that the contaminants necessitate removal of the  
1100 affected lots to prevent an unreasonable risk of substantial harm to the public health and initiates  
1101 the removal two days later. Accordingly, the Combination Product Applicant makes a follow-up

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1102 report to the ICSR that provides the relevant information both for a Five-day report and for the  
1103 product removal as required by 21 CFR Part 806, including the information identified in sections  
1104 V.B.above, and submits the report within 5 work days of determining that the remedial action is  
1105 necessary, which is also within 10 work days of initiating the removal. The Combination  
1106 Product Applicant, thereby, satisfies these additional PMSR requirements.

1107  
1108 Non-ICSR Considerations. Because the applicant included all information required under 21  
1109 CFR Part 806 in its Five-day/follow-up report, a separate correction and removal report is not  
1110 required.

1111  
1112 The Combination Product Applicant determines that a FAR is required because of the  
1113 contamination of the drug coating, which occurred during the manufacturing process. The  
1114 applicant submits a FAR that includes the relevant information, including the information  
1115 identified in section V.B.5 above, within 3 working days of discovering the contamination issue.

1116 **4. Additional Considerations**

1117 In the scenario described above, the contamination issue was discovered as a result of an adverse  
1118 event investigation. Note that had the contamination issue been detected *prior* to any adverse  
1119 event reports, the Combination Product Applicant would first have been required to submit a  
1120 FAR within 3 working days of receiving the information and would also have had to comply  
1121 with other reporting requirements identified in the example, once triggered, by their respective  
1122 timelines.

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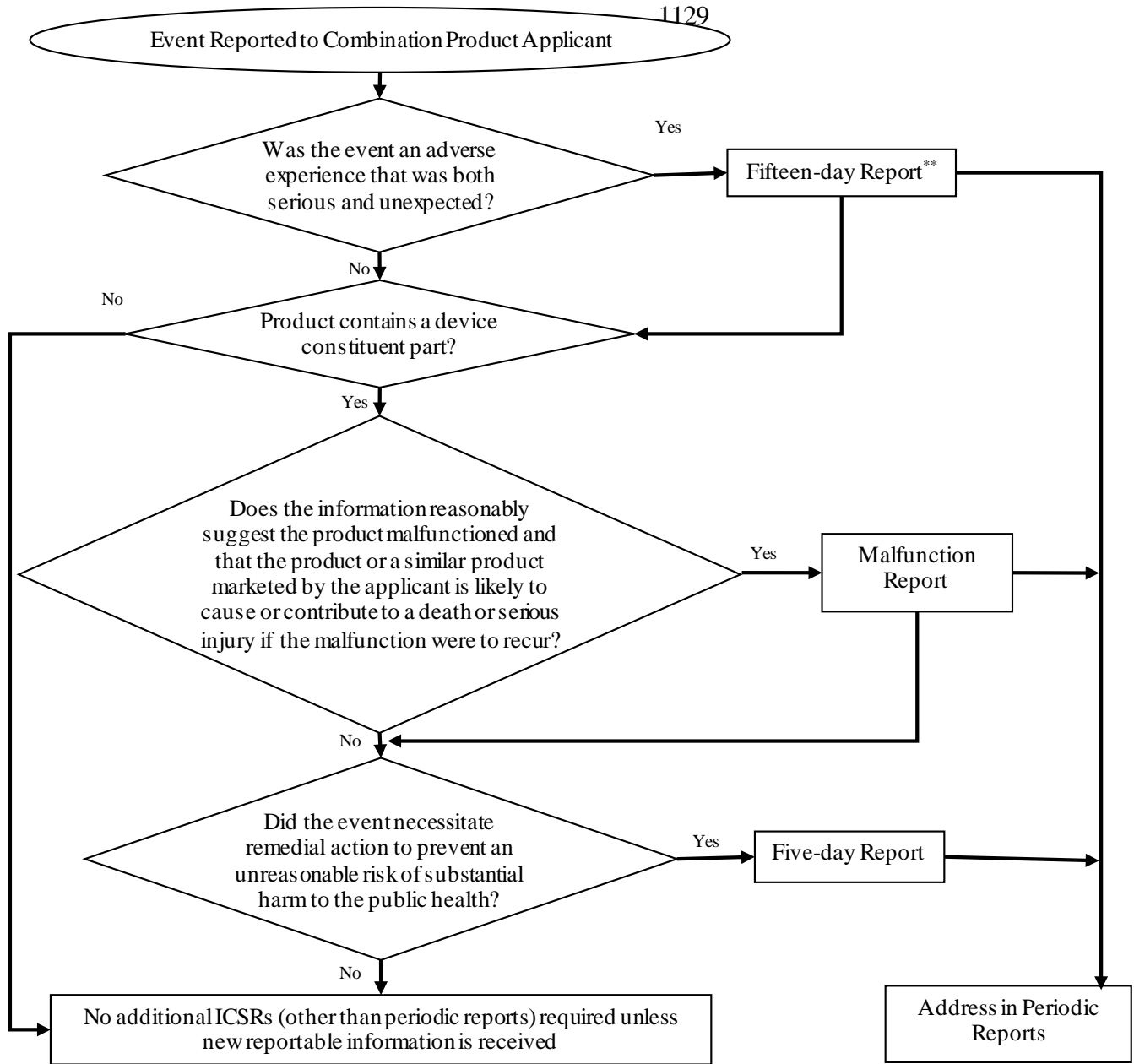
1123 **Appendix 1. Combination Product (CP) PMSR Requirements by Application and Product Type**

Application Type	Applicant's Product Type (CP = Combination Product)	Application Type-Based Requirements			Additional Constituent Part-Based Reporting Requirements (see 21 CFR Section(s))							Other Duties
		See 21 CFR Section(s)			Field Alert Reports 314.81	Fifteen-day Reports 314.80	Biological Product Dev. Reports 600.14 606.171	Fifteen-day Reports 600.80	Five-day Reports 803.3 803.53 803.56	Malfunction Reports 803.50 803.56	Correction and Removal 806.10 806.20	
		314	600 606	803 806								
NDA ANDA	Drug Constituent Part	X			Covered by Application Type-Based Requirements							Share information with other Constituent Part Applicant(s) (21 CFR 4.103)
	Drug-Device CP	X						X	X	X	Address Five-day and Malfunction reports in periodic safety reports (21 CFR 4.102(d))	
	Drug-Biologic CP	X				X	X					
	Drug-Device-Biologic CP	X				X	X	X	X	X	Address Five-day and Malfunction reports in periodic safety reports (21 CFR 4.102(d))	
BLA	Biologic Constituent Part		X		Covered by Application Type-Based Requirements							Share information with other Constituent Part Applicants (21 CFR 4.103)
	Biologic-Device CP		X					X	X	X	Address Five-day and Malfunction reports in periodic safety reports (21 CFR 4.102(d))	
	Biologic-Drug CP		X			X	X					
	Biologic-Drug-Device CP		X			X	X	X	X	X	Address Five-day and Malfunction reports in periodic safety reports (21 CFR 4.102(d))	
Device Application (PMA, 510(k), HDE, PDP, De Novo)	Device Constituent Part			X	Covered by Application Type-Based Requirements							Share information with other Constituent Part Applicants (21 CFR 4.103)
	Device-Drug CP			X		X	X				Provide additional reports only if specified in writing by FDA (21 CFR 4.102(d))	
	Device-Biologic CP			X				X	X			
	Device-Drug-Biologic CP			X		X	X	X	X			

1124

1125 **Appendix 2. Flowcharts for Combination Product ICSR**  
1126 **Requirements**

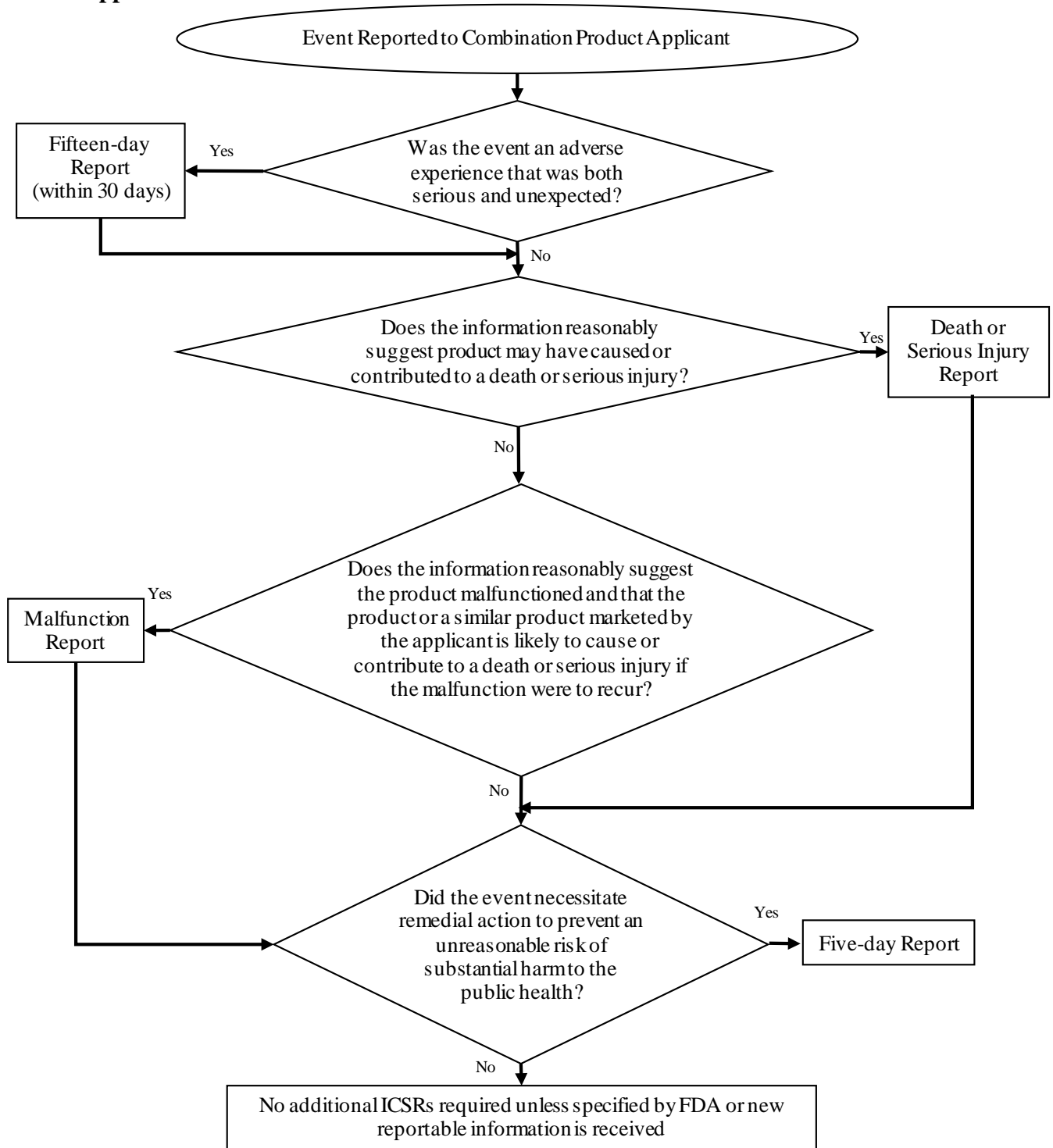
1127 **Chart 2.1. ICSR Reporting Requirements for Combination Products Marketed Under**  
1128 **NDA/ANDA/BLA\***



\* This chart only covers reporting of ICSRs under the combination product PMSR final rule. Other report types (correction and removal report, FAR, BPDR) may also be required. Note options discussed in IV.C for streamlining by combining ICSRs and/or including correction/removal information.

\*\* As was described in the combination product PMSR final rule, because the requirements of 21 CFR 314.80 and 600.80 ensure timely reporting of death and serious injury events for drug and biologic-led combination products, Combination Product Applicants for NDA/ANDA/BLA approved combination products are not required to submit a death or serious injury report under Part 803 (see 81 FR 92613 and section IV.A).

1130 **Chart 2.2. ICSR Reporting Requirements for Combination Products Marketed Under a**  
 1131 **Device Application\***



\* This chart only covers reporting of ICSRs under the combination product PMSR final rule. Other report types (correction and removal report, FAR, BPDR) may also be required. Note options discussed in IV.C for streamlining by combining ICSRs and/or including correction/removal information.

1132  
 1133



1134 **Appendix 3. Combination Product Postmarketing Safety Reporting**  
1135 **Considerations for Entities that are Not “Applicants”**

1136 Entities that are not “Combination Product Applicants” or “Constituent Part Applicants” are not  
1137 subject to the combination product PSMR final rule (see section III.A above). However, such  
1138 entities may be involved in some aspect of the manufacture or marketing of a combination  
1139 product and have postmarketing safety reporting obligations as indicated below:

- 1140 • Manufacturers, packers, and distributors, whose names appear on the label of over-the-  
1141 counter combination products that are not subject to premarket review and include a drug  
1142 constituent part, must comply with the reporting and recordkeeping requirements  
1143 described in section 760 of the FD&C Act (21 U.S.C. 379aa) for the combination  
1144 product.  
1145
- 1146 • Non-applicants listed as a manufacturer, packer, or distributor on the label of a  
1147 combination product that contains a drug or biological product constituent part must  
1148 comply with reporting requirements as described in 21 CFR 314.80 and 600.80 for the  
1149 product, as applicable, but may meet these requirements by instead reporting to the  
1150 applicant within five days of receiving the information and maintaining records of these  
1151 reports as described in 21 CFR 314.80(c)(1)(iii) and 600.80(c)(1)(iii), respectively.  
1152
- 1153 • Manufacturers, packers and distributors of unapproved prescription combination products  
1154 that include a drug constituent part must report and maintain records as described in 21  
1155 CFR 310.305 for the combination product, but packers and distributors may meet these  
1156 requirements by reporting to the combination product manufacturer within five days of  
1157 receiving the information and maintaining records of these reports as described in 21  
1158 CFR 310.305(c)(3).  
1159
- 1160 • Manufacturers, importers, and user facilities (as these terms are defined in 21 CFR  
1161 803.3)<sup>30</sup> for combination products that include a device constituent part (whether or not  
1162 subject to premarket review) must comply with the requirements described in 21 CFR  
1163 Part 803 for the combination product, and may seek exemptions, variances, or  
1164 alternatives to these requirements as described in 21 CFR 803.19(b) (e.g., where there is a  
1165 Combination Product Applicant for the product, other such entities subject to 21 CFR  
1166 Part 803 may seek an exemption from reporting to FDA if they choose instead to report  
1167 to the Combination Product Applicant).  
1168

---

<sup>30</sup> 21 CFR 803.3 defines “manufacturer” as “any person who manufactures, prepares, propagates, compounds, assembles, or processes a [product] by chemical, physical, biological, or other procedure...” Manufacturers include, for example, repackagers, specification developers, accessory manufacturers, and U.S. agents of a foreign manufacturer. See 21 CFR 803.3 for additional definitions, including definitions for “importer” and “device user facility.”

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- 1169           • As defined in 21 CFR 806.2, manufacturers and importers of combination products that  
1170           include a device constituent part must comply with the requirements described in 21 CFR  
1171           Part 806 for the combination product.

1172   If you are such an entity, in complying with the requirements applicable to you, identify the  
1173   product as a combination product and provide a complete discussion of the event with respect to  
1174   the combination product, including each constituent part, as appropriate, based on the  
1175   information available to the entity.

1176

1177 **Appendix 4: Addressing Combination Product ICSR Elements in**  
1178 **Data Fields of Drug and Device Reporting Systems**

1179 **A. Reporting Elements**

1180 The table below identifies which ICSR elements identified in section V.B.2 of this guidance  
1181 should be included in which data field in combination product ICSRs when using the FDA  
1182 Adverse Events Reporting System (FAERS) or eMDR (Electronic Medical Device) reporting  
1183 system. This information is current as of the date of this guidance.<sup>31</sup> Reporters should refer to  
1184 current technical specifications and other documents for detailed instructions for how to  
1185 complete and submit electronic ICSRs.<sup>32, 33</sup>  
1186

Data Element	Form 3500A	eMDR Preferred Term	FAERS DTD Descriptor
Combination Product Identifier	Box G.5	Combination Product	<combinationproductreport>
Report Type(s) (e.g., Fifteen-day, Five-Day)	Box G.7 (15-day, 5-day)	Type_of_Report	<fulfillexpeditecriteria>
Type of Reportable Event	Box H.1 (Malfunction)	Type_of_Reportable_Event	<malfunction>
Patient Identifier	Box A.1	Patient Identifier	<patientinitial>
Reporter Identifier	Box E	Type_of_Reporter	<primarysource>
Suspect Drug Product(s)	Box C.1	Suspect Product(s)	<medicinalproduct> <activesubstancename> <drugauthorizationnumb>
Suspect Medical Device(s)	Box D.2	Common Device Name	<commondevicename>
	Box D.2b	Device Procode	<productcode>
	Box D.1	Brand_Name	<brandname>
Adverse Event Terms	Box H.6 (Device Application) Box G.8 (NDA/ANDA/BLA)	Patient_Problem_Code	<primarysourcereaction>
Device Problem Code	Box H.6	Device_Problem_Code	<evaluationtype> <evaluationvalue>

1187 **B. Reporting Scenario Examples**

1188 The following scenarios are intended to illustrate how information identified in section V.B.2  
1189 above is submitted in ICSRs via the FDA Adverse Event Reporting System (FAERS) for  
1190 NDA/ANDA/BLA combination products and the electronic Medical Device Reporting (eMDR)  
1191 system for Device Application combination products. The scenarios described below are not  
1192 intended to provide a comprehensive representation of all information that must or should be

---

<sup>31</sup> FDA is considering options for providing further assistance to Combination Product Applicants on the issues addressed in this Appendix. We welcome comment on the content of this Appendix and whether additional examples and other mechanisms to communicate this content would be helpful.

<sup>32</sup> See eMDR – Electronic Medical Device Reporting webpage:

<https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/reportingadverseevents/emdr%E2%80%93electronicmedicaldevicereporting/default.htm> for additional information on eMDR.

<sup>33</sup> See FDA Adverse Events Reporting System (FAERS) Electronic Submissions webpage:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm> for additional information on FAERS.

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1193 submitted in ICSRs for a given event, report type, or product type, nor to identify all reports that  
1194 may be required in relation to the events described.

1195 **1. Scenario #1 - FAERS. NDA-approved prefilled on-body infusor.**

1196 Scenario. The Combination Product Applicant for an NDA-approved (NDA 123456) prefilled  
1197 on-body infusor receives information on an event that qualifies as a reportable malfunction, but  
1198 did not involve a patient injury or death. The malfunction was reported by a nurse at XYZ  
1199 General Hospital and involved a software problem where the on-body infusor indicated that a  
1200 dose had been administered when no dose was administered. The applicant must report a  
1201 malfunction within 30 calendar days. The on-body infusor is prefilled with the drug product,  
1202 Drug A, which contains the active ingredient, Active A. The infusor is branded as Infusor A.  
1203

1204 Data Elements.

1205 The Combination Product Applicant searches the Device Product Classification Database  
1206 (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>), but does not find  
1207 any product codes that align with the on-body infusor and therefore does not include the procode  
1208 but does provide a device common name.  
1209

1210 The Combination Product Applicant reviews the Device Problem Codes  
1211 ([https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/  
1212 ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm)) and identifies “Medication  
1213 Error FDA 3198; C91396 Event in which the device software design results in errors of  
1214 medication preparation or administration” as appropriate for the malfunction.  
1215

1216 Because this was a malfunction-only event, there was no adverse patient reaction. For coding  
1217 the adverse event, the Combination Product Applicant does not need to identify an adverse  
1218 patient reaction and can use “None” for patient identifier and “No Adverse Event”<sup>34</sup> in the  
1219 adverse event coding.  
1220

1221 In addition to other appropriate content for the report type, include the following elements in the  
1222 ICSR:  
1223

Type of Information (see section V.B.2 above)	Data Element	DTD Descriptor	Element Value
Combination Product Identifier	A.1.FDA.15	<combinationproductreport>	1 = Yes
Report Type(s)	A.1.9	<fulfillexpeditecriteria>	5 = 30-Day
	A.1.5.FDA.2h	<malfunction>	1 = Yes
Patient Identifier	B.1.1	<patientinitial>	None
	A.2.1.2a	<reporterorganization>	XYZ General Hospital

<sup>35</sup> Reporter can be identified using any of the following data element(s) as applicable: Reporter title (A.2.1.1a <reportertitle>), Reporter given name (A.2.1.1b <reportergivenname>), Reporter middle name (A.2.1.1c <reportermiddlename>), Reporter family name (A.2.1.1d <reporterfamilyname>), Reporter organization (A.2.1.2a <reporterorganization>), Reporter department (A.2.1.2b <reporterdepartment>), Reporter street (A.2.1.2c <reporterstreet>), Reporter city (A.2.1.2d <reportercity>), Reporter state or province (A.2.1.2e <reporterstate>), Reporter postcode (A.2.1.2f <reporterpostcode>), Reporter country code (A.2.1.3 <reportercountry>).

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Reporter Identifier <sup>35</sup>	A.2.1.4	<qualification>	3 = Other Health Professional
Suspect Medical Device	B.4.k.18.6.FDA.1	<brandname>	Infusor A
	B.4.k.18.6.FDA.2	<commondevicename>	On-body Infusor
	B.4.k.18.6.FDA.3	<productcode>	
	B.4.k.18.6.FDA.17	<malfunction>	1 = Yes
	B.4.k.18.6.FDA.19.1a	<evaluationtype>	01 = Device Problem
	B.4.k.18.6.FDA.19.1b	<evaluationvalue>	C91396
Suspect Drug Product	B.4.k.2.1	<medicinalproduct>	Drug A
	B.4.k.2.2	<activesubstancename>	Active A
	B.4.k.4.1	<drugauthorizationnumb>	NDA 123456
Adverse Event Coding	B.2.i.0	<primarysourcereaction>	No Adverse Event

1224                                    **2. Scenario #2 - FAERS. BLA-approved product consisting of one vial of**  
 1225                                    **biological product along with three device constituent parts: 1) syringe, 2) vial**  
 1226                                    **adapter, and 3) sterile needle.<sup>36</sup>**

1227 Scenario. The Combination Product Applicant for BLA 654321 receives information from a  
 1228 physician in California on an adverse experience that was both serious and unexpected  
 1229 (hemorrhage) that resulted in an injury to patient ABC and involved a product malfunction. The  
 1230 serious and unexpected adverse experience was caused by a broken needle during drug delivery.  
 1231 The applicant must submit a Fifteen-day and Malfunction report and does so in a single report  
 1232 submitted within 15 calendar days. After additional information is received, the applicant  
 1233 determines that the product should be removed to prevent an unreasonable risk of substantial  
 1234 harm to the public health and submits a Five-day report as a follow up within 5 work days of  
 1235 determining that remedial action is needed. The biological product, Bio B, contains the Active  
 1236 ingredient, Active B. None of the device constituent parts have brand names.

1237  
 1238 Data Elements

1239 The applicant reviews the Device Product Classification Database  
 1240 (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>) and is able to  
 1241 identify a product code for the syringe (FMF, Syringe, Piston) and the needle (FMI, Needle,  
 1242 Hypodermic, Single Lumen), but is unable to find an appropriate product code for the vial  
 1243 adapter and therefore does not include the procode but does provide a device common name.

1244  
 1245 The applicant reviews the Device Problem Codes  
 1246 (<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm>) and identifies “Fracture  
 1247

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<sup>35</sup> Reporter can be identified using any of the following data element(s) as applicable: Reporter title (A.2.1.1a <reportertitle>), Reporter given name (A.2.1.1b <reportergivenname>), Reporter middle name (A.2.1.1c <reportermiddlename>), Reporter family name (A.2.1.1d <reporterfamilyname>), Reporter organization (A.2.1.2a <reporterorganization>), Reporter department (A.2.1.2b <reporterdepartment>), Reporter street (A.2.1.2c <reporterstreet>), Reporter city (A.2.1.2d <reportercity>), Reporter state or province (A.2.1.2e <reporterstate>), Reporter postcode (A.2.1.2f <reporterpostcode>), Reporter country code (A.2.1.3 <reportercountry>).

<sup>36</sup> When submitting a report that includes both a Fifteen-day and Malfunction report for a combination product with multiple device constituent parts, the narrative should describe the contribution of the combination product and each constituent part to the event to the extent known and identify, if known, which of the constituent parts was involved in the malfunction.

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1248 FDA 1260; C63132 Issue associated with any structural discontinuity in the material; collective  
1249 term for cracks, splitting etc.” as appropriate for the broken needle.

1250  
1251 *Initial ICSR.* In addition to other appropriate content for the report type, include the following  
1252 elements in the initial ICSR:  
1253

Type of Information (see section V.B.2 above)	Data Element	DTD Descriptor	Element Value
Combination Product Identifier	A.1.FDA.15	<combinationproductreport>	1 = Yes
Report Type(s)	A.1.9	<fulfillexpeditecriteria>	1 = 15-Day <sup>37</sup>
	A.1.5.FDA.2h	<malfunction>	1 = Yes
Patient Identifier	B.1.1	<patientinitial>	ABC
Reporter Identifier <sup>38</sup>	A.2.1.2e	<reporterstate>	CA
	A.2.1.4	<qualification>	1 = Physician
Suspect Medical Device	B.4.k.18.6.FDA.2	<commondevicename>	Syringe, Piston
	B.4.k.18.6.FDA.3	<productcode>	FMF
	B.4.k.18.6.FDA.2	<commondevicename>	Needle, Hypodermic, Single Lumen
	B.4.k.18.6.FDA.3	<productcode>	FMI
	B.4.k.18.6.FDA.17	<malfunction>	1 = Yes
	B.4.k.18.6.FDA.19.1a	<evaluationtype>	01 = Device Problem
	B.4.k.18.6.FDA.19.1b	<evaluationvalue>	C63132
	B.4.k.18.6.FDA.2	<commondevicename>	Vial Adapter
Suspect Drug Product	B.4.k.2.1	<medicinalproduct>	Bio B
	B.4.k.2.2	<activesubstancename>	active B
	B.4.k.4.1	<drugauthorizationnumb>	BLA 654321
Adverse Event Coding	B.2.i.0	<primarysourcereaction>	Capillary Hemorrhage

1254  
1255 *Follow-up ICSR.* In addition to other information appropriate for the report type, include all the  
1256 above elements from the initial report AND any additional information for a Five-day report type  
1257 in the follow-up ICSR. As reflected in the chart below, include the element to identify the report

<sup>37</sup> Note that in this example, the Combination Product Applicant submits a Fifteen-day and Malfunction report in a single report submitted within 15 calendar days. Because the report was submitted in 15-days, “1 = 15-day” is used for the <fulfillexpeditecriteria>.

<sup>38</sup> See note 35, *supra*.

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1258 as a 5-Day and use the *same* Manufacturer Control Number (to ensure the report is not  
1259 misidentified in FAERS as an initial report)<sup>39</sup>:  
1260

Type of Information	Data Element	DTD Descriptor	Element Value
Report Types	A.1.9	<fulfillpeditecriteria>	4 = 5-Day
Manufacturer Control Number	A.1.0.1	<safetyreportid>	SAME as Initial Report

1261 **3. Scenario #3 - eMDR. PMA-approved steroid-eluting lead.**

1262 Scenario. The Combination Product Applicant receives information on an adverse experience  
1263 (infection) that was serious, but expected (the product labeling included labeling for such a  
1264 potential adverse event) from patient XYZ that resulted in the need for medical intervention.  
1265 The adverse experience was caused by contamination of the implanted product. The applicant  
1266 submits a serious injury report within 30 calendar days. The product, Implant C, has a coating  
1267 containing the active ingredient, Active C. The product code for the device is DXY (Implantable  
1268 Pacemaker Pulse Generator).

1270 Data Elements

1271 The applicant reviews the Device Problem Codes

1272 ([https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm)  
1273 [ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm)) and identifies “Item  
1274 Contaminated During Manufacturing Or Shipping FDA 2969; C63019 Issue associated with the  
1275 presence of any unexpected foreign substance found on the surface or in the package materials,  
1276 which may affect optimal performance for its intended use” as appropriate for the contamination.  
1277

1278 The applicant reviews the Patient Problem Codes

1279 ([https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm)  
1280 [ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm)) and identifies “Infection  
1281 FDA 1930; C26726 ” as appropriate for the adverse event.  
1282

1283 In addition to other content appropriate for the report type, include the following elements in the  
1284 initial ICSR:  
1285

Type of Information (see section V.B.2 above)	Form 3500A Identifier	eMDR Descriptor	Element Value
Combination Product Identifier	Combination Product [Box G.5]	Combination Product	Yes
Report Type(s)	Type of Report [Box G.7]	Type_of_Report	30-day Report
	Type of Reportable Event [Box H.1]	Type_of_Reportable_Event	Serious Injury
Patient Identifier	Patient Identifier [Box A.1]	Patient Identifier	XYZ

<sup>39</sup> Although not covered as a specific example in this appendix, follow-up reports in eMDR can be submitted and can include a new report type. To identify the report as a follow-up, the applicant would check Box G.7 Follow-up #, and indicate the follow-up number (e.g., Enter 1, if this is the first follow-up report). To add a Five-day report type, for example, the applicant would also check Box G.7 5-day to indicate that this is also a Five-day report. For more information on follow-up reports, see sections IV.A.4 and V.A.2.

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Suspect Medical Device	Brand Name [Box D.1]	Brand_Name	Implant C
	Common Device Name [Box D.2]	Common Device Name	Implantable Pacemaker Pulse Generator
	Procode [Box D.2b]	Device Procode	DXY
Suspect Drug Product	Name [Box C.1]	Suspect Product(s)	Active C
Adverse Event Coding	Patient Code [Box H.6]	Patient_Problem_Code	C26726
Device Problem Code	Device Code [Box H.6]	Device_Problem_Code	C63019

1286  
1287

### C. Including Multiple Entities and/or Multiple Lot Numbers in Combination Product ICSRs

1288 Combination Product Applicants may want to submit information on more than one entity  
1289 involved in the manufacture of the combination product and/or the specific lots of the constituent  
1290 parts that comprise a combination product in their ICSR report. For example:

- 1291
- 1292 • NDA holder PharmaCo is submitting an ICSR for a co-packaged combination product  
1293 where the device constituent part is manufactured by DeviceCo. The device constituent  
1294 part involved in the event was from DeviceCo lot number DEVCO123, and the overall  
1295 co-packaged combination product had lot number COMBO987.

1296  
1297 Include the following information in the ICSR to address the manufacturer and lot  
1298 numbers of the device constituent part and the applicant and lot numbers of the co-  
1299 packaged combination product:

1300

Type of Information	Data Element	DTD Descriptor	Element Value
Combination Product Applicant	B.4.k.4.3	<drugauthorizationholder>	PharmaCo
Device Constituent Part Manufacturer	B.4.k.18.6.FDA.4a	<manufacturename>	DeviceCo
Lot/batch number of the combination product	B.4.k.3	<drugbatchnumb>	COMBO987
Lot/batch number of the device constituent part	B.4.k.18.6.FDA.16	<devicelotnumber>	DEVCO123

- 1301
- 1302 • PMA holder MedCo is submitting an ICSR for a single-entity combination product where  
1303 the combination product lot 123 is manufactured at a facility operated by ContractCo  
1304 rather than by the Combination Product Applicant. The drug constituent part lot 098 is  
1305 supplied from a drug manufacturer and used to manufacture the combination product.

1306  
1307 Include the following information in the ICSR to address the applicant, contract  
1308 manufacturer, and lot numbers of the single-entity combination product, and the lot  
1309 numbers of the drug constituent part:

1310

Type of Information	Form 3500A Identifier	eMDR Preferred Term	Element Value
Combination Product Applicant	Manufacturer Name [Box D.3]	Manufacture Name	MedCo



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Combination Product Manufacturer	Contact Office [Box G.1]	Contact Office	ContractCo
Lot/batch number of the combination product	Lot # [Box D.4]	Lot #	123
Lot/batch number of the drug constituent part	Lot # [Box C.1]	Lot # under Suspect Products	098

1311