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

DRAFT GUIDANCE

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Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 addresses how to comply with the final rule on postmarketing safety[1] 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

[1] 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.

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

II. Background

A. What is a combination product?

A combination product is a product comprised of any combination of a drug, a device, and a biological product.[2] Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.

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

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity. Examples of "single entity" combination products include a prefilled syringe or drug-eluting stent.

- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products. Examples of "co-packaged" combination products include surgical and first-aid kits.

- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose. A light-emitting device that is intended for use with a specific light-activated drug may be an example of such a "cross-labeled" combination product.

- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified

[2] 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).

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

B. How does FDA review and regulate combination products?

A combination product is assigned to an Agency center that will have primary jurisdiction (i.e., the "lead Center") for that combination product's premarket review and regulation. Under section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353(g)(1)), assignment of a combination product to a lead Center is based on a determination of which constituent part provides the primary mode of action (PMOA) of the combination product.[3]

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

C. Summary of the Combination Product PMSR Final Rule

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

- Application Type-Based Reporting Requirements. These requirements apply to *both* Combination Product Applicants and Constituent Part Applicants, based on the application type under which the combination product or constituent part received marketing authorization. (See section III.B.1 for more detailed discussion of application type-based reporting requirements.)

- Constituent Part-Based Reporting Requirements and Streamlining Options. These additional reporting requirements apply *only* to Combination Product Applicants, based

[3] 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)*, at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf.

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

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

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

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

III. General Considerations for Combination Product PMSR Compliance

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

The combination product PMSR final rule applies to two types of "applicants," Combination Product Applicants and Constituent Part Applicants.[4] These terms and the related terms, "applicant" and "application" are defined at 21 CFR 4.101.

[4] 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) 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.

- 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"[5] (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.

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

[5] 21 CFR 4.101.

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

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

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

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

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

- NDAs/ANDAs are subject to the safety reporting requirements described in 21 CFR Part 314

- BLAs are subject to the safety reporting requirements described in 21 CFR Parts 600 and 606

[6] SyringeCo would have its own postmarketing safety reporting obligations that apply to its device.
[7] 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)). 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.
[8] 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.

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

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

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

- NDA/ANDA/BLA for a combination product that contains a device constituent part. The Combination Product Applicant must also comply with:
  - Five-day reporting requirements (see 21 CFR 803.3, 803.53, and 803.56)
  - Malfunction reporting requirements (see 21 CFR 803.50 and 803.56)
  - Correction or removal reporting and recordkeeping requirements for events that do not require a report (see 21 CFR 806.10 and 806.20)

- BLA or Device Application for a combination product that contains a drug constituent part. The Combination Product Applicant must also comply with:
  - Field alert reporting requirements (see 21 CFR 314.81)
  - Fifteen-day reporting requirements (see 21 CFR 314.80[9])

- ANDA/NDA or Device Application for a combination product that contains a biological product constituent part. The Combination Product Applicant must also comply with:
  - Biological product deviation reporting requirements (see 21 CFR 600.14 and 606.171)
  - Fifteen-day reporting requirements (see 21 CFR 600.80)

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

[9] 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).

3. Information sharing requirements apply ONLY to Constituent Part Applicants

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

- Deaths or serious injuries as described in 21 CFR 803.3, or
- Adverse experiences as described in 21 CFR 314.80(a) or 600.80(a).

See 21 CFR 4.103.

IV. Specific PMSR Requirements

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

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

A. Individual Case Safety Reports

Throughout this guidance 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 and 600.80), Five-day

[10] 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.

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

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

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

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

1. Fifteen-day reports (see 21 CFR 314.80 and 600.80) [11]

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

[11] 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.

[12] 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.

[13] 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.

- Adverse experience. An *adverse experience* is any adverse event associated with the use of the combination product, whether or not considered related to the product.[14]

- Seriousness. A *serious adverse experience* is any adverse experience that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the aforementioned outcomes. (see 21 CFR 314.80(a) and 600.80(a).)

- Unexpectedness. An *unexpected adverse experience* is any adverse experience that is not listed in the current labeling for the product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. (see 21 CFR 314.80(a) and 600.80(a).) Whether an event is "expected" for purposes of Fifteen-day reporting is based on whether the event is listed in any current labeling for the combination product including the labeling accompanying each of the constituent parts. For example, if a Combination Product Applicant is marketing a cross-labeled combination product, the labeling accompanying each of the constituent parts would collectively constitute the labeling for the combination product.

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

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

[14] 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 .

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

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

Additional information on adverse experience reporting in the drug context can be found at: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082056.htm.

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

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

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

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

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

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

- Malfunction. When used in the combination product context, "malfunction" means the failure of a device constituent part or the product as a whole to meet its performance specifications or otherwise perform as intended (see 21 CFR 4.102(a) and 803.3(k)). Performance specifications include all claims made in the labeling for the device constituent part or the combination product as a whole (see 21 CFR 4.102(a) and 803.3(k)).

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

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

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

[15] See 21 CFR 803.20(c) regarding what kind of information reasonably suggests an event is or is not reportable.
[16] 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.

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

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

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

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

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

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

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

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

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

5. Combination Product ICSR Information Included in Periodic Safety Reports

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

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

6. Combination Product ICSRs for Foreign Events or Experiences

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

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

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

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

[18] "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)

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

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

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

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

1. Field alert reports (see 21 CFR 314.81)

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

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

A FAR must be submitted even if the issue resulted from material supplied to the applicant by another party. For example, if a Combination Product Applicant whose combination product is approved under a Device Application detects bacteriological contamination and determines that 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.

[19] 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)).

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

Additional information on FARs can be found at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm529734.htm and https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/ucm529890.htm.

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

BPDRs are required for combination products that contain a biological product constituent part (see 21 CFR 4.102(b)(3) and 4.102(c)(3)(i)). BPDRs are required "for any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution," of a product, if that event , either:[20, 21]

- Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or
- Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and
    - Occurs in the applicant's facility or another facility under contract with the applicant; and
    - Involves a distributed product

(21 CFR 600.14 and 606.171).

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

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

[20] 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).

[21] 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).

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

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

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

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

- Removing a combination product from the market because of a manufacturing or design issue that poses a risk to health

- Removing a product from the market because the product contains contaminants that could result in infection or adverse reactions in patients

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

C. Streamlining Reporting

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

- The reports can be submitted in the same manner, *and*

- The combined report satisfies all applicable reporting requirements, including all submission timelines.

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

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

D. Information Sharing Between Constituent Part Applicants

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

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

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

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

For example:

- A cross-labeled combination product is composed of a drug constituent part being marketed under an NDA held by one Constituent Part Applicant, and a device constituent part being marketed under a Device Application held by the other Constituent Part Applicant. The drug Constituent Part Applicant receives information that during use of the combination product, a patient received a severe skin burn. The drug Constituent Part Applicant must forward to the device Constituent Part Applicant that initial information received by the drug Constituent Part Applicant regarding the event.

- A cross-labeled combination product is composed of a delivery device constituent part marketed under a Device Application held by one Constituent Part Applicant and of a drug constituent part marketed under an NDA held by the other Constituent Part Applicant. The device Constituent Part Applicant receives information on a device constituent part malfunction that did not occur during patient use and did not result in a death, serious injury, or other adverse experience. The device Constituent Part Applicant must report the event to FDA as appropriate under 21 CFR Part 803 reporting obligations, but is not required to share the information with the drug Constituent Part Applicant because no serious injury, death or other adverse experience occurred.

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

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

E. Recordkeeping Requirements

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

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

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

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

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

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

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

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

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

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

V. Process Considerations for Combination Product Applicants

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

A. How to Submit Combination Product PMSR Information to FDA

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

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

Table 1. Timelines for Various Combination Product PMSR Requirements

Report Type	Timeline for Reporting
Fifteen-day Reports	No later than 15 calendar days 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 30 calendar days from initial receipt of information by the applicant (see 21 CFR 4.102(c))
Follow-ups to Fifteen-day Reports	Within 15 calendar days 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 30 calendar days from initial receipt of the information by the applicant (see 21 CFR 4.102(c)).
Five-day Reports	No later than 5 work days after the day that you become aware of the event (see 21 CFR 803.53)
Death/Serious Injury/Malfunction Reports	No later than 30 calendar days 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 30 calendar days of the day that you receive the information (see 21 CFR 803.56)
Field Alert Reports	Within 3 working days 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 45 calendar days 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 10 working days of initiating correction or removal (see 21 CFR 806.10(b))

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

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

2. Where/how do I submit reports?

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

Accordingly, for:

- A Device Application combination product, submit all ICSRs (including Fifteen-day reports) in accordance with 21 CFR 803.12(a) and associated guidance

- An NDA or ANDA combination product, submit all ICSRs (including Five-day reports and Malfunction reports if the combination product includes a device constituent part) in accordance with 21 CFR 314.80(g) and associated guidance

- A BLA combination product, submit all ICSRs (including Five-day reports and Malfunction reports if the combination product includes a device constituent part) in accordance with 21 CFR 600.80(h) and associated guidance

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

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

For additional information on reporting, see:

- ICSRs:
  - Draft Guidance for Industry, *Providing Submissions in Electronic Format — Postmarketing Safety Reports*, which, when final, will represent FDA's current thinking on this topic (https://www.fda.gov/downloads/drugs/guidances/ucm072369.pdf).

802 - Implementation specifications for CDRH eMDR, found at:
803 https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Postmarket
804 RequirementsReportingAdverseEvents/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/surveillan
809 ce/adversedrugeffects/ucm115894.htm)
810
811 • Field Alert Reports:
812 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/uc
813 m529729.htm
814 https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformati
815 on/ucm529890.htm
816
817 • Recalls, Corrections and Removals:
818 https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequiremen
819 ts/recallscorrectionsandremovals/default.htm
820
821 • Biological Product Deviation Reports:
822 https://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/biological
823 productdeviations/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.

B. What Information to Include in Combination Product PMSR Reports[22]

1. General content when submitting combination product PMSR reports

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

2. Additional information to include in combination product ICSRs

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

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

- Combination Product Identifier. Indicate that the report is for a combination product.

- Report Type(s). Identify the type of report. If one report is being made to cover multiple reporting requirements, each report type should be identified (e.g., if the report covers both Fifteen-day and Malfunction reporting requirements, the appropriate identifier should be included for each report type).

[22] 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.

[23] 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).

[24] 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.

- 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 (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[25] (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 of patient problem codes or the submitter may enter descriptive term (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/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[26] or "No adverse event."

- Device Problem Code. Identify at least one device problem code. FDA maintains an online list of device problem codes

[25] 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) for assistance, as well as OCP as needed.

[26] 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/electronicsubmissions/ucm153588.pdf).

(https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm). If there is no device problem associated with the ICSR, enter the device code for "No Known Device Problem" for this field.

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

3. Information to include in Follow-up ICSRs

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

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

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

[27] Submitting follow-up ICSRs consistent with the applicable regulations, policies, and procedures associated with the application type comports 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.

[28] 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.

[29] 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).

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

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

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

When submitting a correction and removal report:

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

When submitting a FAR:

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

When submitting a BPDR:

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

VI. Examples

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

A. Drug application combination product

1. Product Description and Scenario

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

2. Initial ICSR Reporting

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

- Was the event an adverse experience that was both serious and unexpected?

  YES. The event was both serious and unexpected (was not included in the product labeling). A Fifteen-day report is required.

- Does the product contain a device constituent part? YES.

- Did the report reasonably suggest that the product malfunctioned and that the product or a similar product marketed by the applicant would be likely to cause or contribute to a death or serious injury if the malfunction were to recur?

  YES. The report indicated that the device did not perform as intended, which resulted in temporary blindness. A Malfunction report is required.

- Did the event necessitate remedial action to prevent an unreasonable risk of substantial harm to the public health?

  NO. At the time of the initial report, no information is available to the Combination Product Applicant to indicate that a remedial action is necessary to prevent an unreasonable risk of substantial harm. A Five-day report is not required at this time.

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

3. Reporting based on Additional Information Received

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

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

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

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

4. Additional Considerations for this Scenario

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

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

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

B. Device Application combination product

1. Product Description and Scenario

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

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

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

2. Initial ICSR Reporting

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

- Was the event an adverse experience that was both serious and unexpected?

  YES. The serious infection was a serious adverse experience that was unexpected because the severity of the event exceeds any of the warnings on the product labeling. A Fifteen-day report (made within 30 calendar days) is required.

- Is the event a reportable death or serious injury?

  YES. Medical intervention was required to address potentially life-threatening risk to the patient after the event. A serious injury report is required.

- Did the event necessitate remedial action to prevent an unreasonable risk of substantial harm to the public health?

  NO. Review of the production records showed no anomalies in the manufacturing process or lot for the product. No other information available to the applicant indicates that a remedial action is necessary at this time. No Five-day report is required.

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

3. Reporting based on Additional Information Received

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

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

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

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

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

4. Additional Considerations

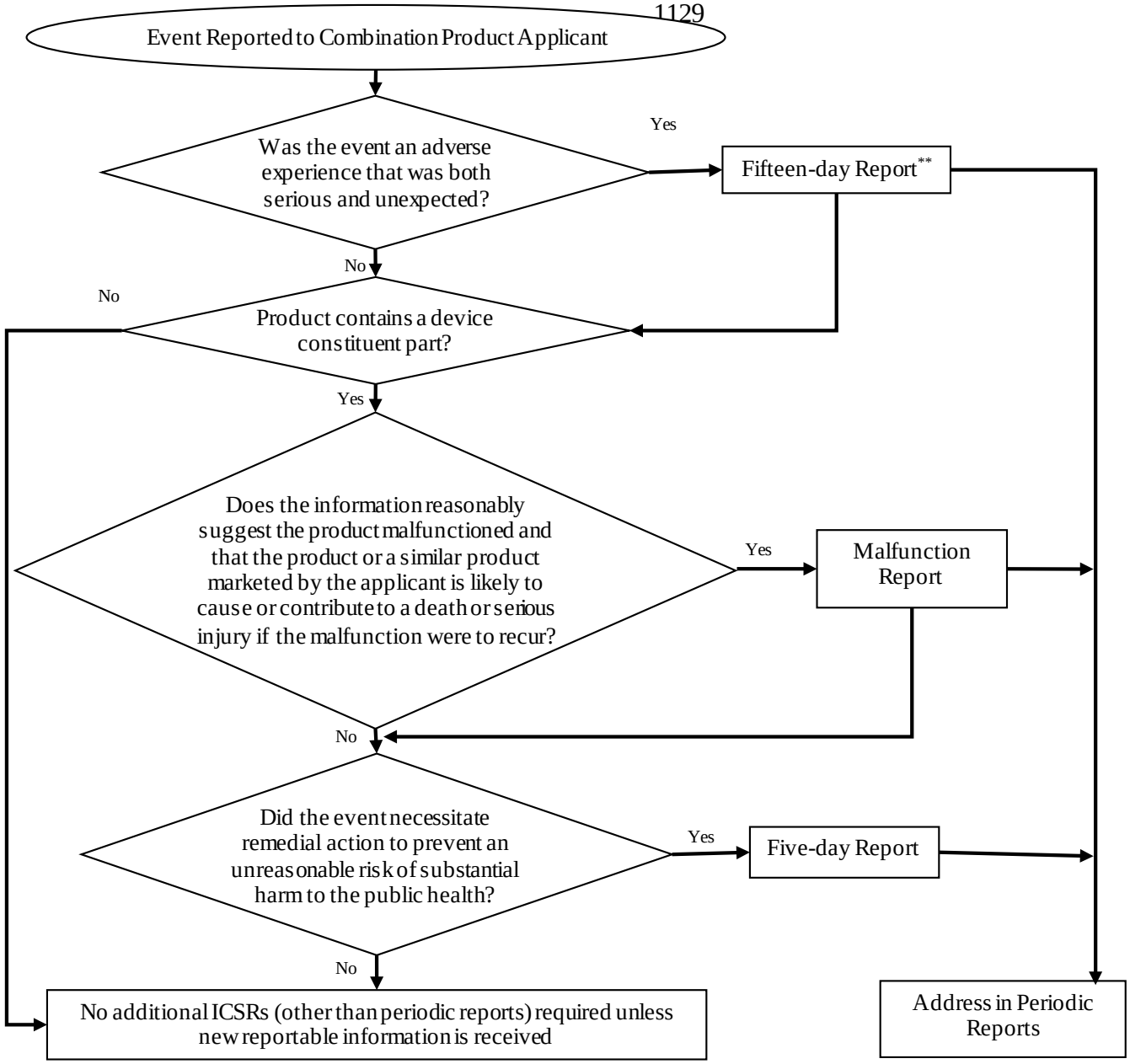
In the scenario described above, the contamination issue was discovered as a result of an adverse event investigation. Note that had the contamination issue been detected *prior* to any adverse event reports, the Combination Product Applicant would first have been required to submit a FAR within 3 working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

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: See 21 CFR Section(s) 314	600 606	803 806	Additional Constituent Part-Based Reporting Requirements (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	Other Duties
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				

Appendix 2. Flowcharts for Combination Product ICSR Requirements

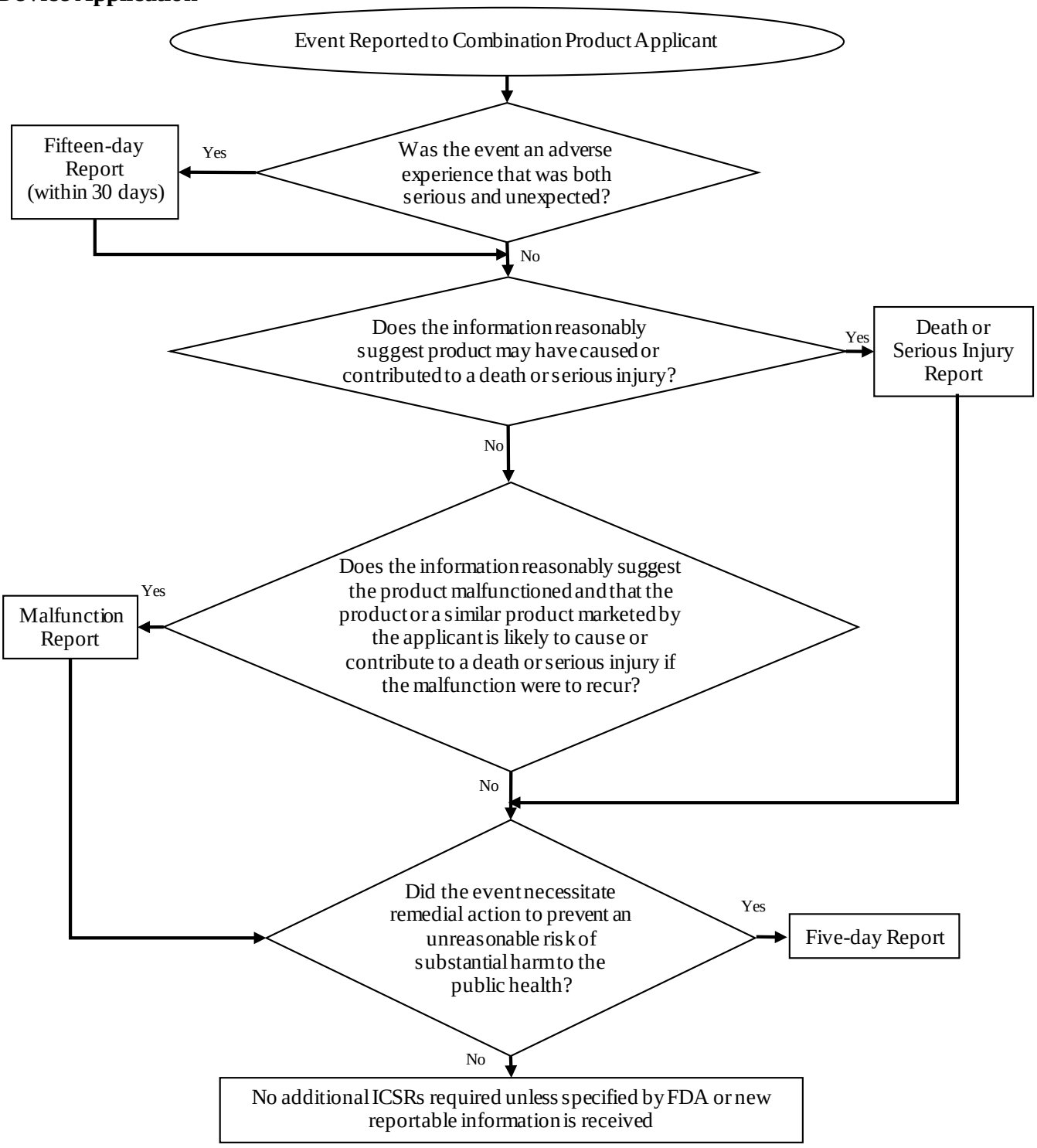
Chart 2.1. ICSR Reporting Requirements for Combination Products Marketed Under NDA/ANDA/BLA*



* 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).

Chart 2.2. ICSR Reporting Requirements for Combination Products Marketed Under a 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.

Appendix 3. Combination Product Postmarketing Safety Reporting Considerations for Entities that are Not "Applicants"

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

- Manufacturers, packers, and distributors, whose names appear on the label of over-the-counter combination products that are not subject to premarket review and include a drug constituent part, must comply with the reporting and recordkeeping requirements described in section 760 of the FD&C Act (21 U.S.C. 379aa) for the combination product.

- Non-applicants listed as a manufacturer, packer, or distributor on the label of a combination product that contains a drug or biological product constituent part must comply with reporting requirements as described in 21 CFR 314.80 and 600.80 for the product, as applicable, but may meet these requirements by instead reporting to the applicant within five days of receiving the information and maintaining records of these reports as described in 21 CFR 314.80(c)(1)(iii) and 600.80(c)(1)(iii), respectively.

- Manufacturers, packers and distributors of unapproved prescription combination products that include a drug constituent part must report and maintain records as described in 21 CFR 310.305 for the combination product, but packers and distributors may meet these requirements by reporting to the combination product manufacturer within five days of receiving the information and maintaining records of these reports as described in 21 CFR 310.305(c)(3).

- Manufacturers, importers, and user facilities (as these terms are defined in 21 CFR 803.3)[30] for combination products that include a device constituent part (whether or not subject to premarket review) must comply with the requirements described in 21 CFR Part 803 for the combination product, and may seek exemptions, variances, or alternatives to these requirements as described in 21 CFR 803.19(b) (e.g., where there is a Combination Product Applicant for the product, other such entities subject to 21 CFR Part 803 may seek an exemption from reporting to FDA if they choose instead to report to the Combination Product Applicant).

[30] 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."

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

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

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

A. Reporting Elements

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

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	<evaulation type> <evaluationvalue>

B. Reporting Scenario Examples

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

[31] 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.
[32] 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.
[33] 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.

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

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

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

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

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

Because this was a malfunction-only event, there was no adverse patient reaction. For coding the adverse event, the Combination Product Applicant does not need to identify an adverse patient reaction and can use "None" for patient identifier and "No Adverse Event"[34] in the adverse event coding.

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

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

[35] 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 <reportergivename>), 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>).

Reporter Identifier[35]	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

2. *Scenario #2 - FAERS. BLA-approved product consisting of one vial of biological product along with three device constituent parts: 1) syringe, 2) vial adapter, and 3) sterile needle.*[36]

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

Data Elements

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

The applicant reviews the Device Problem Codes (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm) and identifies "Fracture

[35] 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 <reportergivename>), 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>).

[36] 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.

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

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

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[37]
	A.1.5.FDA.2h	<malfunction>	1 = Yes
Patient Identifier	B.1.1	<patientinitial>	ABC
Reporter Identifier[38]	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
	B.4.k.18.6.FDA.3	<productcode>	
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

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

[37] 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>.
[38] See note 35, *supra*.

as a 5-Day and use the *same* Manufacturer Control Number (to ensure the report is not misidentified in FAERS as an initial report)[39]:

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

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

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

Data Elements

The applicant reviews the Device Problem Codes (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm) and identifies "Item Contaminated During Manufacturing Or Shipping FDA 2969; C63019 Issue associated with the presence of any unexpected foreign substance found on the surface or in the package materials, which may affect optimal performance for its intended use" as appropriate for the contamination.

The applicant reviews the Patient Problem Codes (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm) and identifies "Infection FDA 1930; C26726 " as appropriate for the adverse event.

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

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

[39] 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.

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 [BoxD.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

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

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

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

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

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	<manufacturername>	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

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

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

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

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