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

FINAL GUIDANCE

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TABLE OF CONTENTS

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

I. Introduction

This guidance addresses certain ways to comply with the final rule on postmarketing safety[1, 2] reporting (PMSR) requirements for combination products that FDA issued on December 20, 2016 (81 FR 92603) and that is codified in 21 CFR Part 4, Subpart B (hereafter the "combination product PMSR final rule," "final rule," or "rule"). 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 rule addresses PMSR requirements for combination products that have received FDA marketing authorization, to ensure consistent and complete reporting while avoiding duplication.

Section II of the guidance provides general information on combination products and how FDA regulates them. Section III provides a summary of the combination product PMSR final rule and an overview of which entities are subject to the final rule and what safety reporting requirements apply to them. 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 certain ways to comply with certain combination product PMSR requirements. While this guidance focuses on 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 federal register notice for 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.

[2] Note additional statutory or regulatory requirements may apply in relation to postmarket safety events, such as relevant submission and review requirements for postapproval modifications for example. Neither the PMSR rule nor this guidance is intended to alter such requirements or Agency policy concerning them.

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 composed of any combination of a drug, a device, and a biological product.[3] 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 composed 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, transdermal patch, or drug-eluting stent.

- Two or more separate products packaged together in a single package or as a unit and comprising 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 investigational drug, device, or biological product where both are required to achieve

[3] Applicants and FDA generally resolve whether a product is a combination product, or a constituent part of a combination product, as defined in 21 CFR Part 3, prior to approval or clearance of the application. Whether you are seeking marketing authorization or your product is already cleared or approved, if you are uncertain of whether it is a combination product or a constituent part of a combination product or its Center assignment, we encourage you to contact the Office of Combination Products (OCP). If you wish to obtain a binding 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/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd), or if you wish to obtain informal feedback, 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/regulatory-information/search-fda-guidance-documents/how-prepare-pre-request-designation-pre-rfd).

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 regulation, including for ensuring compliance with postmarketing regulatory requirements. 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.[4] If, for example, the PMOA of a device-biological product combination product is attributable to the biological product constituent part, the center responsible for premarket review of such a biological product would have primary jurisdiction for the regulation of the combination product.

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 with the other center(s) and the Office of Combination Products (OCP), as appropriate, in light of the issues raised and expertise needed, on review of PMSR information and any responses to the submitter.

III. General Considerations for Combination Product PMSR Compliance

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 elements 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. Constituent part-based reporting requirements apply *only* to Combination Product Applicants and are based 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.)

[4] 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 (see 21 USC 353(g)(1)(C) and 21 CFR 3.2(m); see also 21 CFR 3.2(k) (defines "mode of action")). 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/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd.

- 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. 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.)

- Streamlined reporting. The rule offers means to satisfy certain reporting requirements together in the same report. (See sections IV.C and V.A.3 for detailed discussion of streamlined reporting opportunities and methods.)

- 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.)

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 (21 CFR 4.100(a)).[5] These terms and the related terms, "applicant" and "application" are defined at 21 CFR 4.101.

- Applicant and Application. 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"[6] (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)).

- Combination Product Applicant means the applicant that holds the only application or all applications for a combination product.[7] (Note that the Combination Product Applicant holds the application, but may not be the manufacturer, e.g., if the combination product is manufactured by a contract manufacturer.) Following are examples of Combination Product Applicants:
    - A company that holds an approved PMA for a drug-eluting stent (a single-entity combination product).

[5] There are other 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. Entities with questions regarding how to comply with reporting requirements applicable to non-applicants should contact the lead Center or OCP, as needed.
[6] 21 CFR 4.101.
[7] *Id*.

  - A company that holds an approved NDA for a pre-metered dry powder 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 in a pre-filled syringe configuration (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, together, compose a cross-labeled combination product).

- Constituent Part Applicant means an applicant that 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.[8] Generally, there would be Constituent Part Applicants if the combination product is marketed by two different entities in a cross-labeled configuration. For example, where a laser system (device) and light-activated drug compose 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 for this combined use.
  - The separate entity that holds the approved NDA for the light-activated drug for this combined use.

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.

- If one company holds the applications to market products for use together as 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 compose a cross-labeled combination product), then that company is the Combination Product Applicant, and there are no Constituent Part Applicants.

- If 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.

- A company 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

[8] *Id*.

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.[9] Rather, PharmaCo is *the* Combination Product Applicant for the co-packaged combination product, and there are *no* Constituent Part Applicants for the combination product.[10]

B. What Safety Reporting Requirements Apply to Me if I Am a Combination Product Applicant or Constituent Part Applicant?

This section summarizes safety reporting requirements associated with the constituent parts of combination products (i.e., 21 CFR Part 314 requirements for drugs, 21 CFR Parts 600 and 606 requirements for biological products, and 21 CFR Parts 803 and 806 requirements for devices), and the information sharing requirements that ply to Constituent Part Applicants under the rule.[11, 12] (See also Appendix 1, which provides a summary table of the PMSR requirements in the final rule applicable to the various types of Combination Product and Constituent Part Applicants, and section IV for additional discussion of the PMSR requirements specified in the rule for Combination Product Applicants.)

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[9] SyringeCo would have its own postmarketing safety reporting obligations under 21 CFR Part 803 that apply to its device.

[10] 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; see also Guidance for Industry and FDA Staff, *Current Good Manufacturing Practice Requirements for Combination Products* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products) (providing guidance on requirements imposed by regulation)). 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.

[11] Although investigational combination products are not subject to the combination product PMSR final rule, if the combination product or constituent part used in the clinical investigation is already legally marketed, entities must report adverse events that occur in the investigational setting as required by the PMSR requirements that apply to that entity for that marketed combination product or constituent part. For example, if a Combination Product Applicant is legally marketing a drug-device combination product under an NDA and receives a report of a malfunction that occurred during investigation of that combination product for a new use, that Combination Product Applicant must report the malfunction to FDA under 21 CFR 4.102(c)(1)(ii) (see also section IV.A.3). 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/regulatory-information/search-fda-guidance-documents/medical-device-reporting-manufacturers) and Guidance for Industry and Investigators, *Safety Reporting Requirements for INDs and BA/BE Studies* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-reporting-requirements-inds-investigational-new-drug-applications-and-babe). Entities with questions regarding how to comply with reporting requirements applicable to investigational combination products should contact the lead Center or OCP, as needed.

[12] 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.

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 their combination product or constituent part received marketing authorization (21 CFR 4.102(b)). 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
- 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)). (See section IV below for more detailed discussion, including streamlined reporting opportunities.)

Reporting under a single application. Listed below are the additional reporting requirements Combination Product Applicants must meet based on the types of constituent parts in the combination product and the application type for the combination product:

- NDA/ANDA/BLA for a combination product that contains a device constituent part. The Combination Product Applicant must also comply with (21 CFR 4.102(c)(1)):
  - 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 and 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 (21 CFR 4.102(c)(2)):
  - Field alert reporting (FAR) requirements (see 21 CFR 314.81)
  - Fifteen-day reporting requirements (see 21 CFR 314.80[13])

[13] The reporting requirements under 21 CFR 314.80 and 600.80 are equivalent. Combination products with both drug and biological product constituent parts need not submit separate Fifteen-day reports to comply with each requirement. Submitting a single Fifteen-day report containing the required information is sufficient (see also section IV.A.1).

- ANDA/NDA or Device Application for a combination product that contains a biological product constituent part. The Combination Product Applicant must also comply with (21 CFR 4.102(c)(3)):
    - Biological product deviation reporting (BPDR) requirements (see 21 CFR 600.14 and 606.171)
    - Fifteen-day reporting requirements (see 21 CFR 600.80[13])

Reporting under separate applications. If 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 and processes 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 to the extent such information is available.[14]

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 receipt, initial information received on the following events associated with the combination product (see section IV.D for more detailed discussion):

- Deaths or serious injuries as described in 21 CFR 803.3, and
- 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 in greater detail certain PMSR requirements under the final rule. Sections IV.A and IV.B describe the constituent part-based reporting requirements applicable to Combination Product Applicants (see 21 CFR 4.102). Section IV.C describes means for Combination Product Applicants 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 for Combination Product Applicants and Constituent Part Applicants (see 21 CFR 4.105). (The process requirements for submitting reports under 21 CFR 4.104 are addressed in section V.)

With regard to PMSR for Combination Product Applicants, this discussion is not meant to describe every reporting requirement but rather to help these entities understand PMSR requirements not associated with the application type for their product, with which they may be

[14] In addition to the information required under the applicable regulations, the Combination Product Applicant should include the Combination Product Identifier and, in the narrative, the application number for the other constituent part(s).

less familiar, and to highlight considerations specific to combination products for complying with PMSR requirements. 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.[15] Rather, this section focuses on information-sharing and record-keeping requirements for these applicants.

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. Accordingly, the entire combination product and each constituent part should be considered in determining whether a report is required and what information to include. For clarity, adjustments have been made in the discussion of these requirements in sections IV.A and B below, such as using the term "product" in place of the term "drug," "biological product," or "device."

A. Individual Case Safety Reports for Combination Product Applicants

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 reports (see 21 CFR 803.3, 803.53, and 803.56), Malfunction reports (see 21 CFR 803.50 and 803.56), and reports of deaths or serious injuries (see 21 CFR Part 803).[16]

Please note that each of the sections below discusses circumstances under which the specified report type may be required for Combination Product Applicants. 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.

[15] However, it is important to note that Constituent Part Applicants should consider events in their entirety, including the events' implications for the safe and effective use of the combination product as a whole, to ensure they provide complete, comprehensive reporting for their constituent part.

[16] Note that death and serious injury reporting requirements (see 21 CFR Part 803) are not explained in this section 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 do not explain the reporting of non-expedited (non-Fifteen-day) ICSRs under 21 CFR 314.80 and 600.80 in this section 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.

(See also Appendix 2, presenting flowcharts illustrating how to determine whether ICSRs must be submitted by Combination Product Applicants under the combination product PMSR final rule.)

1. Fifteen-day Reports (see 21 CFR 314.80 and 600.80)[17]

Fifteen-day reporting requirements apply to combination products that contain a drug or biological product constituent part (see 21 CFR 4.102(b)(2) and (b)(3) and 4.102(c)(2)(ii) and (c)(3)(ii)).[18] Combination Product Applicants must submit Fifteen-day reports for:

- "adverse experiences" that are both "serious" and "unexpected"[19]
- within fifteen calendar days for combination products marketed under an ANDA, NDA, or BLA
- or within 30 calendar days for combination products marketed under a Device Application, as explained below.[20]

(See 4.102, 314.80(a) and (c), and 600.80(a) and (c).)

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.[21]

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

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[17] 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.

[18] 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/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-human-drug-and-biological-products-including-vaccines) which, when final, will represent the FDA's current thinking on this topic.

[19] 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/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-human-drug-and-biological-products-including-vaccines) which, when final, will represent the Agency's current thinking on this topic.

[20] 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/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-human-drug-and-biological-products-including-vaccines) which, when final, will represent the Agency's current thinking on this topic.

[21] 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.

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 accompanying the combination product, including any labeling accompanying individual constituent parts. For a cross-labeled combination product, if the event is listed in the labeling accompanying either of the constituent parts, the event is considered expected.

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 (an unlabeled adverse event), 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 (see 21 CFR 4.102(c)(2)(ii) and (c)(3)(ii)). 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 (see sections IV.C and V.B.2 below for further discussion).[22]

Combination products that contain both a drug and biological product constituent part(s). 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 for the same event. The Fifteen-day reporting requirements are equivalent in 21 CFR 314.80 and 600.80 and submitting a single Fifteen-day report containing the required information is sufficient (see sections IV.C and V.A.3 below for further discussion).

Additional information on adverse experience reporting in the drug context can be found at: https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs.

[22] While FDA anticipates such scenarios will be rare, 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, 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.

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

Five-day reporting requirements apply to combination products that contain a device constituent part (21 CFR 4.102(b)(1) and 4.102(c)(1)(i)).

Combination Product Applicants for such combination products must submit Five-day reports no later than five work days after the day the Combination Product Applicant becomes aware[23] 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
- 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, a Five-day report would be required in the following scenario. The applicant for a prefilled rescue inhaler approved under an NDA determines that a reportable adverse event was caused by a design flaw that causes the inhaler actuator to fail and the drug to not be delivered. The design flaw is known to be present in the product in the field, and the product in the field can fail in the same manner, likely resulting in life-threatening injury or death (which would pose an unreasonable risk of substantial harm to the public health). Once the applicant determines that it is necessary to remove the product from the market until the design can be corrected (i.e., becomes aware that remedial action is necessary to prevent an unreasonable risk of substantial harm to the public health), it must file a report within five work days (see 21 CFR 803.53).

Likewise, a Five-day report would be required under 21 CFR 803.53 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 sections IV.B.3 below for additional discussion of correction and removal reports and streamlining of these reports with Five-day reports).

[23] Applicants are considered to have become aware when any employee with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or whose duties relate to the collection and reporting of adverse events, becomes aware, from any information, including any trend analysis, that a reportable event or events necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health (see 21 CFR 803.3(b)). If FDA has requested Five-day reports for certain events in accordance with 21 CFR 803.53(b), applicants are also considered to have become aware when any employee becomes aware of such an event occurring (see 21 CFR 803.3(b)).

Note, submission of a Five-day report (or correction or removal report) does not alter an applicant's obligation to submit other postmarketing safety reports for the product. Applicants must continue to assess events, and report them to FDA as required, in accordance with all the PMSR requirements applicable to the product.

Additional information on Five-day reports can be found at: https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

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

Malfunction reporting requirements apply to combination products that contain a device constituent part (see 21 CFR 4.102(b)(1), 4.102(c)(1)(ii), 803.50, and 803.56).

Combination Product Applicants for such combination products must submit Malfunction reports no later than 30 calendar days[24] after the applicant receives or otherwise becomes aware of information that:

- "Reasonably suggests"[25]
- 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).

  Malfunction. When used in the combination product context, "malfunction" means the failure of a device constituent part or of 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 for the combination product as a whole (see 21 CFR 4.102(a) and 803.3(k)).

  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 the information reasonably

[24] Note, an altenative, voluntary program for reporting of malfunctions is available for certain combination products see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

[25] Under 21 CFR 803.20(c), any information, including professional, scientific, or medical facts, observations, or opinions, may reasonably suggest that a product has caused or may have caused or contributed to a reportable event.

suggests that an adverse experience (see footnote 21 and associated text) that was both serious and unexpected was caused or contributed to by the malfunction (see 21 CFR 4.102(c)(1)(ii), 314.80, 600.80, and 803.50).

For example, a Combination Product Applicant determines that a Fifteen-day report is required after a serious unexpected adverse 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) and should be submitted as a follow-up report to the initial Fifteen-day report, identified as a Malfunction report.[26] FDA does not intend to object if the report is submitted within 30 calendar days after the day the applicant becomes aware of the reportable malfunction (see also section IV.A.4 below discussing follow-up reports).[27]

A Malfunction report may also be required when a Fifteen-day report is not. For example, an NDA applicant receives a report that a medical professional noticed before use 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 if the breach in the sterile barrier would be likely to cause or contribute to a death or serious injury (such as an infection requiring hospitalization for treatment of the infection) if it were to recur (see 21 CFR 4.102(c)(1)(ii) and 803.50). Likewise, if an NDA applicant receives a report that the needle of an auto-injector deployed early and no dose, or a partial dose, was delivered, the NDA applicant must submit a Malfunction report if the product would be likely to cause or contribute to a serious injury or death if the malfunction recurred, even if there was no patient injury or death associated with the reported malfunction event (see 21 CFR 4.102(c)(1)(ii) and 803.50).[28]

Additional information on Malfunction reports can be found at: https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

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

[26] Follow-up reports should be submitted consistent with the technical instructions for the applicable FDA adverse event reporting system. See Section V.A.2 for information on FDA Adverse Event Reporting Syste (FAERS), Elecronic Medical Device Reporting System (eMDR), and Vaccine Adverse Event Reporting System (VAERS).

[27] Note that had the Combination Product Applicant become aware of the reportable malfunction before submitting the Fifteen-day report, it could have submitted a single report within 15 days to meet both requirements (see also Section V.A.3 below).

[28] Reportable malfunctions (as well as reportable death and serious injuries) may involve medication errors such as in this example of partial or missed dose. Medication errors are events that are preventable and may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer, see https://www.fda.gov/drugs/drug-safety-and-availability/medication-errors-related-cder-regulated-drug-products. When submitting malfunction reports that involve medication errors, the applicant should include related medication error Reaction/Event codes or Device/Patient Problem codes (see Section V.B.2) and a discussion of the medication error in the narrative section of the report.

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 of receipt of the new information for Fifteen-day reports for combination products marketed under an ANDA, NDA, or BLA (see 21 CFR 314.80 and 600.80) (but see "Use of follow-up reports to satisfy different types of ICSR requirements" below). 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 (see 21 CFR 314.80). For combination products marketed under a Device Application, follow-up reports for Fifteen-day, Five-day, Malfunction, and death or serious injury reports must be submitted within 30 calendar days (see 21 CFR 4.102(c)(2)(ii), 4.102(c)(3)(ii), and 803.56), though the Combination Product Applicant may choose to submit follow-up reports on or before the due date.

Use of follow-up reports to satisfy different types of ICSR requirements.[29] If a Combination Product Applicant submits an initial Malfunction report and later determines that a Fifteen-day report must also be submitted for that event, the Combination Product Applicant should submit the Fifteen-day report as a follow-up report to the initial Malfunction report. The same approach should be used if the initially submitted report was a Fifteen-day report or a non-expedited ICSR required under 21 CFR 314.80(c)(2)(ii)(B) and 600.80(c)(2)(ii)(B) (for serious and expected, and nonserious, adverse experiences), and the Combination Product Applicant later determines that a Malfunction report is also required; the applicant should submit the Malfunction report as a follow-up to the initial report.

Note that for a drug or biologic-led combination product, the Agency does not intend to object if the applicant submits the Malfunction report as a follow-up to the previously submitted Fifteen-day report within 30, rather than 15, calendar days after the day the applicant becomes aware of information that a reportable malfunction also occurred. A Malfunction report for an event that was originally reported in a non-expedited ICSR must be submitted within 30 calendar days after the day the applicant becomes aware of information that reasonably suggests that a reportable malfunction also occurred, and follow-up reports for the malfunction are required when the applicant becomes aware of reportable new information on the malfunction (see 21 CFR 4.102(c)(1), 803.50, and 803.56). (See also Section V.B.3 discussing information to include in follow-up reports.)

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 (21 CFR 4.102(d)(1), see 21 CFR 314.80(c)(2) and 600.80(c)(2)). If such a combination product includes a device constituent part,

[29] If a Five-day report is required related to a previously submitted ICSR, due to the public health significance, the Five-day report should be submitted as an initial report.

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 report(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 (see 21 CFR 4.102(d)(2)). 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 for such events (see 21 CFR 4.102). In addition, even to the extent it may not be required to be reported under FDA regulations, we recommend the reporting of foreign events for products marketed outside the U.S., as discussed further below, to enhance awareness and understanding of safety considerations that may be relevant to U.S. combination products, as for other medical products.

General considerations. Combination Product Applicants are not expected to report on foreign events that did not involve their product (for example, if they can confirm that the event was instead associated with another applicant's product). When reporting an event for a product marketed only outside the U.S., the Combination Product Applicant should include the foreign trade name/brand name, and should submit that information in a manner consistent with the process for the lead Center. See also Section V.B.2 regarding information to include in combination product ICSRs.

Fifteen-day Reports. Combination Product Applicants must submit Fifteen-day reports for foreign experiences consistent with the requirements for drugs and biological products (see 21 CFR 4.102(b) and (c), 314.80(c)(1) and 600.80(c)(1)). Specifically, foreign reports of serious, unexpected adverse experiences must be submitted as Fifteen-day reports (see 21 CFR 4.102(b) and (c), 314.80(c)(1) and 600.80(c)(1)). Combination Product Applicants should also submit Fifteen-day reports for events associated with foreign products that they market that have the same active moiety (or active ingredient for biological product constituent parts) as the U.S.-marketed product,[30] even if the formulation, dosage form, strength, or route of administration of the foreign-marketed product is different than that of the U.S.-marketed product. For example, if in the U.S. the applicant markets only a prefilled syringe of a drug containing an active moiety, and outside the U.S. the applicant markets an oral dosage form containing the same active moiety, the applicant should report adverse events that are both serious and unexpected for that oral dosage form to the FDA and reference the U.S. product application number in the report.

[30] For additional information see Draft Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-human-drug-and-biological-products-including-vaccines) which, when final, will represent the FDA's current thinking on this topic.

Device ICSRs. Consistent with the approach for devices, Combination Product Applicants for combination products containing device constituent parts should submit Malfunction reports to FDA for otherwise reportable malfunctions, for both devices and device constituent parts of combination products marketed outside the U.S. by that applicant that are the same as, or similar to, the device constituent part of the applicant's U.S.-marketed combination product if the malfunction is likely to occur in the U.S.-marketed combination product.[31,32] For combination products marketed under a Device Application, Combination Product Applicants should also submit death and serious injury reports for foreign events for both devices and device constituent parts of combination products marketed outside the U.S. by that applicant that are the same or similar to the device constituent part of the applicant's U.S.-marketed combination product if such event is likely to occur in the U.S.-marketed combination product. For purposes of this guidance, FDA considers a device or device constituent part of a combination product marketed outside the U.S. by the applicant to be similar to the device constituent part of the applicant's U.S.-marketed combination product if the device or device constituent part of the combination product marketed outside the U.S. by the applicant:[33]

- Is of the same type (e.g., would have the same product code) as the device constituent part of the applicant's U.S.-marketed combination product;
- Has the same basic design and performance characteristics related to safety and effectiveness as the device constituent part of the applicant's U.S.-marketed combination product; and
- Is for the same general purpose and function as the device constituent part of the applicant's U.S.-marketed combination product.

Devices and device constituent parts of combination products marketed outside the U.S. that differ only in minor features unrelated to safety or effectiveness (e.g., as may be the case for different sizes or other minor design changes to the device constituent part of the U.S.-marketed combination product) can be considered similar. Devices and device constituent parts of combination products may be manufactured to slightly modified specifications to meet standards in different countries. If such device or device constituent part is similar to the device constituent part of the U.S.-marketed combination product, as described above, then any events that would otherwise require an ICSR should be reported if the event is likely to occur in the U.S.-marketed combination product.

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[31] See Guidance for Industry and FDA Staff, *Medical Device Reporting for Manufacturers* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-reporting-manufacturers)

[32] If a malfunction occurs with a U.S.-marketed combination product, and the criteria in 21 CFR 803.50 are met, then a Malfunction report must be submitted to the FDA, regardless of whether the event occurs in the U.S.

[33] The considerations described here for a same or similar device or device constituent part are aligned with related content in the Guidance for Industry and FDA Staff, *Medical Device Reporting for Manufacturers* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-reporting-manufacturers). The language from the guidance has been adapted to facilitate application to combination products that contain a device constituent part and is not intended to alter the discussion of foreign reporting for devices in the *Medical Device Reporting for Manufacturers* guidance.

Examples. A Combination Product Applicant:

- That markets a coronary drug-eluting stent (DES) in the U.S. should submit Malfunction reports for otherwise reportable malfunctions regarding DES deformation for a coronary DES coated with a different antiproliferative drug that the applicant markets outside the U.S. if that DES differs only in size from, and is otherwise similar to (as described above), the DES marketed in the U.S., and the malfunction is likely to occur in the U.S.-marketed combination product.

- Should submit Malfunction reports for foreign events involving otherwise reportable malfunctions of needle-stick prevention features for the applicant's prefilled syringe marketed outside the U.S., if (i) there are only minor differences in the needle-stick prevention features of its pre-filled syringe marketed in the U.S. that do not change the basic design and performance characteristics of the syringe as related to safety and effectiveness, and (ii) the malfunction is likely to occur in the U.S.-marketed combination product.

  However, the recommendation to submit Malfunction reports for foreign events would not apply with respect to failures of needle-stick prevention features when such features of its foreign-marketed syringes are not the same as or similar to that of a syringe that is part of its U.S. marketed combination product. For example, if the foreign-marketed prefilled syringe uses a hinged recapping feature whereas the design used in the syringe in the U.S.-marketed combination product is a sliding sleeve, malfunction reports involving failures of the hinged recapping feature in the foreign-marketed product would not be relevant for the U.S.-marketed combination product and therefore the recommendation for malfunction reporting would not apply.

- Should submit Malfunction reports for foreign events involving otherwise reportable malfunctions of a similar inhaler with a drug cartridge, relating to a user's inability to deliver a dose. For example, the Combination Product Applicant should submit a report if (i) the inhaler has only minor differences (e.g., minor differences in the shape of the external housing) as compared to the inhaler used in the applicant's U.S.-marketed combination product, and (ii) the malfunction is likely to occur in the U.S.-marketed combination product.

  However, the recommendation to submit Malfunction reports related to foreign events would not apply with respect to clogged inhaler nozzles if the basic design and performance characteristics related to safety and effectiveness of the inhaler in the foreign-marketed product are different because in such cases, the malfunction is not likely to occur in the inhaler of the U.S.-marketed combination product. For example, the recommendation to submit Malfunction reports would not apply if the blockage results from the actuator nozzle orifice having a diameter that is significantly smaller, i.e., that significantly alters performance in the inhaler of the foreign marketed product, as compared to the inhaler in the U.S.-marketed product.

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

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

Please note that each of the sections below discusses circumstances under which the specified report type may be required.[34] These discussions are not intended to identify all reports that may be required in relation to the events described, and the reports 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)

Field alert reporting requirements apply to distributed combination products that contain a drug constituent part (see 21 CFR 4.102(b)(2) and 4.102(c)(2)(i)). See also sections IV.C and V.A.3 below regarding streamlining of FAR and BDPR reporting.

Combination Product Applicants for such combination products must submit FARs within three working days of receipt of information for:

- "[A]ny 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
- "[A]ny failure of one or more distributed batches of the [product] to meet the specification established for it in the application" (21 CFR 314.81).

We also recommend that Combination Product Applicants submit additional information, including updates, as it becomes available.[35]

A FAR is required for any of the issues described above that could have resulted from the manufacturing process for any of the constituent parts of the combination product or for the combination product (see 21 CFR 4.102(a) and 314.81). A FAR must be submitted even if the issue resulted from material supplied to the applicant by another party (21 CFR 314.81 makes no distinction on this basis).

For example, bacteriological contamination of a distributed 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 (see 21 CFR 4.102 and 314.81).

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[34] Although not specifically discussed in this section, submittal of additional information may be required after submission of a non-ICSR report (see, e.g., 21 CFR 806.10(c)(13) and (d)). .

[35] For additional information on follow-up reports to FARs, see *Field Alert Report Submission Questions and Answers Draft Guidance for Industry* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/field-alert-report-submission-questions-and-answers-guidance-industry) which, when final, will represent the FDA's current thinking on this topic).

Likewise, if the coating on a distributed drug-eluting stent does not meet specifications because of impurities introduced during formulation of the coating or the stent coating process, or because of impurities on the metal stent, a FAR must be submitted (see 21 CFR 4.102 and 314.81). In addition, if the impurities were due to a drug product received from a supplier, the Combination Product Applicant 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/surveillance/field-alert-report-form-questions-and-answers and https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/submitting-field-alert-reports-fars-cber.

2. Biological Product Deviation Reports (see 21 CFR 600.14 and 606.171)

Biological product deviation reporting requirements apply to distributed combination products that contain a biological product constituent part (see 21 CFR 4.102(b)(3) and 4.102(c)(3)(i)). See also sections IV.C and V.A.3 below regarding streamlining of FAR and BDPR reporting.

Combination Product Applicants for such combination products must submit BPDRs 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:[36, 37]

- Represents either —
  - 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
  - an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product;
- 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).

BPDRs may be required when there are manufacturing process deviations for the combination product. For example, a BPRD is required if there is a manufacturing deviation that could

[36] 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/regulatory-information/search-fda-guidance-documents/biological-product-deviation-reporting-licensed-manufacturers-biological-products-other-blood-and).

[37] See also Guidance for Industry, *Biological Product Deviation Reporting for Blood and Plasma Establishments* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biological-product-deviation-reporting-blood-and-plasma-establishments).

impact the purity of a recombinant bone morphogenetic protein in a distributed PMA-approved bone graft combination product (see 21 CFR 4.102(c)(3)(i) and 600.14).

An event that triggers a BPDR can be related to any of the constituent parts. For example, a BPDR would be required if a distributed BLA-approved prefilled syringe of a vaccine incorporates a syringe component that does not meet required materials specifications and that deviation may affect the safety, purity, or potency of the vaccine (see 21 CFR 4.102(a) and 600.14).

3. Correction and Removal Reports (see 21 CFR 806.10)

Correction and removal reporting requirements apply to combination products that contain a device constituent part (21 CFR 4.102(b)(1), (c)(1)(iii), and 806.10).

Combination Product Applicant for such combination products must submit reports of corrections and removals:

- Within 10 working days of initiating a correction or removal, to
- "[R]educe a risk to health posed by the [product]" or
- "[R]emedy a violation of the [FD&C Act] caused by the [product] which may present a risk to health" (21 CFR 806.10).

  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)).

For example, a report would be required when removing a combination product from the market to address a design issue that poses a risk of injury to the user or removing a product from the market due to contaminants that could result in infection or adverse reactions in patients (see 21 CFR 4.102 and 806.10).

The Combination Product Applicant must submit a written report to FDA of any reportable correction or removal of the combination product (see 21 CFR 4.102(b) and (c)), 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 806.10).

See note at section IV.A.2 regarding continuing obligation to comply with all PMSR requirements even after submission of a correction or removal report.

C. Streamlined Reporting for Combination Product Applicants

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 streamlined reporting is available for submitting multiple types of ICSR, ICSRs and correction and removal reports, and FARs and BPDRs.

D. Information Sharing Between Constituent Part Applicants

Information sharing requirements apply to Constituent Part Applicants (21 CFR 4.103). Under 21 CFR 4.103, Constituent Part Applicants must share information:

- No later than 5 days from receipt;
- 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 information must be shared regardless of whether the event is expected or unexpected and regardless of whether the Constituent Part Applicant believes it involves only its constituent part (see 21 CFR 4.103). The definition of "adverse experience" includes death and serious injuries (see 21 CFR 314.80(a) and 600.80(a)). However, other events may constitute adverse experiences (see footnote 21 and associated text).

21 CFR 4.103 requires sharing of only initial information received. 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, nor to share additional information received regarding the event, though FDA recommends such continued coordination to help ensure informed, effective reporting to the Agency.

No information on other events is required to be shared. 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.

Other PMSR duties apply. 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.

Examples:

- 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 the initial information it receives on the event to the device Constituent Part Applicant (see 21 CFR 4.103). Each applicant must report the event to FDA if required under the reporting requirements applicable to its constituent part.

- A cross-labeled combination product is composed of a drug 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 result in a death, serious injury, or other adverse experience. The device Constituent Part Applicant is not required to share the information with the drug Constituent Part Applicant because no serious injury, death or other adverse experience occurred, but must report the event to FDA as appropriate under 21 CFR Part 803.

Constituent part status and information sharing. As reflected in footnote 3 above, applicants that are uncertain of whether their products are constituent parts of combination products 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 entities to share such information with one another regardless of whether such sharing is required or the products necessarily compose a combination product.

E. Recordkeeping Requirements for Combination Product and Constituent Part Applicants

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

1. Constituent Part Applicants

Constituent Part Applicants are subject to separate recordkeeping requirements with regard to their reporting and their information sharing requirements. These recordkeeping requirements are as follows:

- Retain reporting-related records for the time periods stipulated in the regulations applicable to the type of constituent part (see 21 CFR 4.102(b) and 4.105(a)(1)), and
- Retain information-sharing records 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)).
- Information sharing records 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 (see 21 CFR 4.103(b)).

Examples. Consider the following scenarios relating to PharmaCo, which holds an NDA for a drug constituent part of a combination product, and MedCo, which 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 the required records of sharing the information with MedCo for 10 years from the date PharmaCo received the information because the only PMSR recordkeeping period applicable to PharmaCo is 10 years for adverse drug experiences (see 21 CFR 4.105(a)(2) and 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 instance, for malfunction, 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,[38] whichever is greater, in accordance with the recordkeeping requirements under 21 CFR Part 803.

MedCo receives and shares with PharmaCo information about another adverse experience associated with administration of the combination product:

- MedCo must retain the required records of sharing the information for the longest of the record retention periods applicable to MedCo for the device constituent part, which

[38] Under 21 CFR 803.3(f), the expected life of the device "means the time that a device is expected to remain functional after it is placed into use. Certain implanted devices have specified 'end of life' (EOL) dates. Other devices are not labeled as to their respective EOL, but are expected to remain operational through activities such as maintenance, repairs, or upgrades, for an estimated period of time."

would be the longer of 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 (see 21 CFR 4.105(a)(2)).

- PharmaCo would again have to retain this information for the 10-year record-keeping period applicable to it for all adverse experiences for its drug constituent part (see 21 CFR 314.80(j)).

2. Combination Product Applicants

Combination Product Applicants must retain PMSR records for the longest time period required for records under all PMSR requirements applicable to the combination product (see 21 CFR 4.105(b)). Therefore:

- For drug-biologic combination products, this period is 10 years (see 21 CFR 314.80(j) and 600.80(k)).

- For combination products that include a device constituent part, this period would be the longer of either 10 years or 2 years beyond the expected life of the product (see 21 CFR 314.80(j), 600.80(k), 803.18, 806.20).

  For example, if an implantable drug-device combination product has an expected life of 3 years, the longest applicable recordkeeping requirement would be 10 years. Conversely, if that combination product has an expected life of 9 years, the longest applicable recordkeeping requirement would be the expected life plus two years (equaling 11 years in this case).

V. Process Considerations for Combination Product Applicants

The sections below discuss regulatory requirements under the final rule, and provide guidance to Combination Product Applicants,[39] 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) and footnote 42).

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 receive marketing authorization under a Device Application, Fifteen-day reports under 21 CFR 314.80 or 600.80 can be submitted within 30

[39] For Combination Product Applicants marketing constituent parts under separate applications, see also Section III.B.2.

calendar days, rather than within 15 calendar 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	ANDA, NDA, and BLA combination products: 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)). Device Application combination products: 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*	ANDA, NDA, and BLA combination products: Within 15 calendar days of receipt of new information (see 21 CFR 314.80(c) and 600.80(c)).** Device Application combination products: No later than 30 calendar days from initial receipt of new information by the applicant (see 21 CFR 4.102(c)).
Five-day Reports	No later than 5 work days after the day that the applicant "becomes aware" (see footnote 23) that a reportable event(s) necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health (see 21 CFR 803.53).
Death/Serious Injury/Malfunction Reports	No later than 30 calendar days after the day that the applicant receives information or otherwise becomes aware of the event (see 21 CFR 803.50)
Supplemental/ Follow-up reports to Five-day/ Death/ Serious Injury/ Malfunction Report*	Within 30 calendar days of the day that the applicant receives 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 follow-up reports may be used to submit a different type of ICSR for the same event

** See section IV.A.4 above, which discusses the submission of follow-up reports to Fifteen-day reports for malfunctions related to the same event in 30 rather than 15 days.

2. Where/how do I submit reports?

ICSRs (including Follow-up Reports). Combination Product Applicants must submit ICSRs in accordance with the procedural requirements in the regulations associated with the application type (see 21 CFR 4.104(b)) 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; and

- 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.

For example, if the combination product received marketing authorization under a Device Application, submit Fifteen-day reports and 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/medical-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities/health-level-seven-hl7-individual-case-safety-reporting-icsr-files).

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

For additional information on reporting, see:

- ICSRs:
  - FDA Adverse Event Reporting System (FAERS) Electronic Submissions (https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions).
  - Electronic Medical Device Reporting (eMDR) (https://www.fda.gov/industry/fda-esubmitter/electronic-medical-device-reporting-emdr)
  - Implementation specifications for CDRH eMDR (https://www.fda.gov/medical-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities/health-level-seven-hl7-individual-case-safety-reporting-icsr-files)
  - Technical specifications for CBER/CDER electronic ICSRs, contained in *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (https://www.fda.gov/media/111763/download)

  - CBER Vaccine ICSR Implementation (includes information on the Vaccine Adverse Event Reporting System or VAERS) (https://www.fda.gov/industry/about-esg/cber-vaccine-icsr-implementation)

- Non-ICSRs:
  - Field Alert Reports: https://www.fda.gov/drugs/surveillance/field-alert-reports and https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/submitting-field-alert-reports-fars-cber
  - Recalls, Corrections and Removals: https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices
  - Biological Product Deviation Reports: https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/general-instructions-completing-biological-product-deviation-report-bpdr-form-fda-3486

3. How can I streamline reporting for the same event?

ICSRs. Combination Product Applicants may submit a single ICSR rather than separate reports to comply with multiple reporting requirements that are appropriately met through an ICSR for the same event (see section IV.C above). For example:

- Assume a Combination Product Applicant who holds an approved NDA for a drug-device combination product must submit both a Fifteen-day (see 21 CFR 314.80) and Malfunction (see 21 CFR 803.50) report for an event. That applicant could satisfy both requirements by submitting a single report within 15 days that includes all of the information required in both types of reports for the event (see 21 CFR 4.102(b) and (c)).[40]

Correction/Removal in ICSR. Combination Product Applicants may report a correction or removal through a serious injury or death report (for Device Application combination products), Fifteen-day report, Malfunction report, or Five-day report (see 21 CFR 4.102 and 806.10(f); see also 81 FR at 92612-13 and 92615). For example:

- Assume a Combination Product Applicant who holds an approved PMA for a device-biological product combination product must submit a Five-day (see 21 CFR 803.3 and 803.53) and correction or removal (see 21 CFR 806.10) report. The applicant can satisfy both of these requirements by submitting a single report that contains all required information and is submitted no more than 5 work days after determining that remedial action was needed (see 21 CFR 4.102(b), 803.53, and 806.10(f)).

[40] Combination Product Applicants for drug and biologic-led combination products are also required to submit non-expedited ICSRs (ICSRs for adverse experiences that are either serious and expected or nonserious) (see 21 CFR 4.102(b), 314.80, and 600.80). If a Combination Product Applicant for a drug or biologic-led combination product is required to submit a Malfunction report and a non-expedited ICSR for an event, the applicant could submit a single report within 30 days that includes all of the information required in both types of reports for the event (see 21 CFR 4.102(b) and (c), 314.80, 600.80, and 803.50).

Non-ICSRs—FARs and BPDRs. If an event for a distributed combination product that includes a drug and a biological product constituent part requires submission of both a FAR and BPDR, FDA does not intend to object if the Combination Product Applicant submits a single report for both the FAR and BPDR provided that the report:

- Is designated either as a FAR for an NDA/ANDA combination product or as a BPDR for a BLA combination product,
- Contains sufficient information about the event and the combination product, including relevant information about both the drug and biological product constituent parts (e.g., trade name, active ingredient(s), dosage form, strength) and the issues triggering both a FAR and BPDR,
- Is submitted in accordance with the procedures of the lead Center, and
- Is submitted within the shorter time-frame (i.e., within the 3-working day time-frame for a FAR, as opposed to the 45-calendar day time-frame for a BPDR).

We encourage Combination Product Applicants interested in establishing procedures for submitting such combined FAR/BPDR reports to discuss the approach with the lead Center or OCP.

B. What Information to Include in Combination Product PMSR Reports[41]

1. General Content when Submitting Combination Product PMSR Reports

PMSR reports for combination products:

- Must contain all information required for the report type under the applicable regulations, including relevant information on the entire product (including each constituent part) (21 CFR 4.102), and
- In situations where the Combination Product Applicant submits multiple types of reports for the same event or product problem, the reports should include references to related PMSR reports, including previously filed PMSR reports, consistent with the reporting policies and practices of the lead Center.

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, to enable efficient, effective evaluation.[42] Please see technical specifications and instructions for

[41] See also footnote 24.

[42] For ICSRs submitted by Constituent Part Applicants, in addition to the information required under the applicable regulations for their product type, include the Combination Product Identifier and, in the narrative, the application number for the other constituent part(s).

the various ICSR reporting mechanisms for specific details on how to complete and submit reports.[43]

The following information should be provided, including the information regarding constituent parts of the combination product, regardless of which constituent part(s) may have been 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(s), you should include the information on the device constituent part(s) of the combination product.

See also https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products for examples illustrating the reporting of the information below to FDA reporting systems (FAERS, etc).

- Combination Product Identifier. Indicate that the report is for a combination product. If an applicant markets a product in both a non-combination and combination product configuration (e.g., the same drug packaged with and without a syringe), the combination product identifier should only be included for events that occurred with the combination product configuration.[44]

- Report Type(s). Identify the type of report(s). If one submission 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 of these report types).

- Patient Identifier. Provide a patient identifier. If there was no patient involved in the event (e.g., if a malfunction occurred and no patient was involved), enter "None."

- Reporter Identifier. Identifier for the individual that provided the report to the Combination Product Applicant.

- Suspect[45] Medical Device. Include the procode that most closely aligns with the device constituent part(s), as well as the device common name and/or brand name as applicable.[46]

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[43] While FDA has identified in this section information that Combination Product Applicants should include in ICSRs to help ensure that FDA has complete information on the product and the event, the reporting systems also allow Combination Product Applicants to address additional data elements. Combination Product Applicants are encouraged to submit content on these additional data elements as well, when available (see section V.A.2 for information on FAERS, eMDR, and VAERS).

[44] If an event is not initially identified as involving a combination product, but additional information received after the report is submitted indicates that the event involved the combination product, the combination product identifier should be submitted in a follow-up report.

[45] For purposes of combination product ICSRs, the term "Suspect Medical Device" and "Suspect Drug or Biological Product" do not mean that the identified constituent part is necessarily implicated in the event. These fields are used to identify the constituent parts of the overall "Suspect" combination product involved in the event. The contribution of any constituent part to the event should be described in the narrative.

[46] Please note, while this information is helpful for efficient review of ICSRs for all combination products with a device constituent part, selection of a procode for device constituent parts of ANDA/NDA/BLA combination

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). Some common procodes for device constituent parts of ANDA/NDA/BLA combination products are provided at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products. The Combination Product Applicant may contact CDRH's Division of Industry and Consumer Education (DICE) (DICE@fda.hhs.gov), as well as OCP, as needed for assistance in determining the product code that most closely aligns with their device constituent part. If there is not a procode that closely aligns with the device constituent part, enter the device common name and/or the brand name. Include this device constituent part information regardless of whether you believe the device constituent part was implicated in the event.[47]

- Suspect Drug or Biological Product(s). Enter the known product attributes for the drug or biological product constituent part(s) (e.g., trade name, active ingredient(s), dosage form, strength). Include these drug or biological product attributes regardless of whether you believe the drug or biological product constituent part was implicated in the event. For NDA/ANDA/BLA approved combination products, include the combination product's application number in this field.

- Adverse Event Coding.
  - For Device Application combination products, enter at least one Patient Problem Code, or a descriptive term if there is no code. FDA maintains a list of patient problem codes (https://www.fda.gov/medical-devices/mdr-adverse-event-codes/coding-resources).
  - 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[48] or "No adverse event."

- Device Problem Code. Identify at least one device problem code. FDA maintains a list of device problem codes (https://www.fda.gov/medical-devices/mdr-adverse-event-codes/coding-resources).[49] If there is no device problem associated with the ICSR, enter the device code for "No Known Device Problem" for this field.

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products does not indicate the device constituent part is classified within that generic type of device nor whether the device constituent part would be classified within that generic type if marketed independently.

[47] For combination products that include multiple device constituent parts (e.g., kits of devices co-packaged with a drug), each of the device constituent parts should be identified. If all device constituent parts are contained within the same procode (e.g., a needlestick prevention device attached to a prefilled syringe, both of which are covered by procode MEG), then only that single procode should be included. Information regarding any contribution of individual device constituent parts to the event should be addressed in the narrative.

[48] For additional information on use of MedDRA coding, see *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (https://www.fda.gov/media/76569/download).

[49] CDRH also maintains a list of "evaluation codes" that provides information if the applicant evaluated the device constituent part or combination product.

3. Information to Include in Follow-up ICSRs

In determining what information to include in follow-up ICSRs, you must follow applicable regulations. We also recommend that you follow applicable policies and procedures associated with the application type for the combination product.[50] For example, for Device Application combination products, include only new, changed or corrected information (see 21 CFR 803.56(c)). For NDA/ANDA/BLA combination products, the follow-up ICSR should include relevant information from the initial report combined with the new information.[51] Note if using a follow-up report to submit a different type of ICSR (e.g., to submit a Malfunction report related to a previously submitted Fifteen-day report), include all additional information for that report type. See 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. Information to Include in Periodic Safety Reports for ANDA/NDA/BLA Combination Products that Include a Device Constituent Part

Addressing Five-day and Malfunction reports. Periodic adverse drug experience reports (PADERs) and periodic adverse experience reports (PAERs) for ANDA/NDA/BLA combination products must address information from any initial and follow-up Five-day and Malfunction reports, in addition to any from Fifteen-day reports, submitted during the reporting interval, and should provide this information 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 format (e.g., ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)[52]) instead of 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), 314.80(c)(2)(ii) and 600.80(c)(2)(ii)) and should provide this information in the body of the report or as an appendix.

(https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/ucm584205.htm). When such evaluation is performed for combination products, the evaluation codes, as well as a summary of the evaluation, is required to be included in a serious injury or death report, Malfunction report, or Five-day report, and if that information becomes available after such initial report, then that information must be included in a follow-up report to such initial report (see 21 CFR 803.52(f)(3) and (f)(6)). However, for NDA/ANDA/BLA combination products, FDA does not intend to object if the applicant does not provide the evaluation codes, but instead provides evaluation information in the narrative.

[50] 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.

[51] For additional information, see Draft Guidance for Industry, *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-human-drug-and-biological-products-including-vaccines) which, when final, will represent the FDA's current thinking on this topic.

[52] For more information about PBRER, see Guidance for Industry, *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2cr2-periodic-benefit-risk-evaluation-report-pbrer).

Analysis of Five-day and Malfunction reports versus Fifteen-day reports. The summary and analysis of Five-day and Malfunction reports should be presented separately from the summary and analysis of Fifteen-day reports. Applicants should provide separate summary tabulations for Malfunction and for Five-day reports, respectively, that were reported during the reporting interval, regardless of whether the malfunction or Five-day reportable action related to an adverse event. These tabulations should include device problem codes and any adverse event terms that were included in Malfunction or Five-day reports, with counts of occurrences for each. If a Malfunction or Five-day report related to an adverse event (e.g., the event required both a Fifteen-day and Malfunction report), the adverse event should also be accounted for in the summary tabulations for adverse events.

Any questions on periodic safety 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 information required to be included in the type of report, we recommend that the following information also be included.

When submitting a correction or removal report, the report should:

- 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 correction or removal. With respect to the device constituent part(s), the report should include the device product code.
- Include the Combination Product Applicant name, address, telephone number, and contact person (if not otherwise required to be included in the correction or removal report).

When submitting a FAR, the report should:

- 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 with the issue. If the product includes a device constituent part(s), the report should include at least one of the following: the device product code, the device common name and/or the brand name.

When submitting a BPDR, the report should:

- 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 with the issue. If the product includes a device constituent part(s), the report should include at least one of the following: the device product code, the device common name and/or the brand name.

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 had difficulty pulling back the syringe plunger rod and when he managed 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 (see 21 CFR 4.102 and 314.80).

- 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 (see 21 CFR 4.102 and 803.50).

- 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, insufficient information is available to the Combination Product Applicant to determine whether 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 (see 21 CFR 314.80 and 803.50, respectively). The Combination Product Applicant provides a report that includes the required information for a Fifteen-day and Malfunction report (see 21 CFR 314.80 and 803.52, respectively), as well as the information recommended in section 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 (and prior to initiating the removal), the Combination Product Applicant submits a Five-day report to comply with this reporting requirement (see 21 CFR 4.102 and 803.53).

Non-ICSR PMSR Considerations. The Combination Product Applicant determines that the change in material 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 lots of the combination product were not meeting the specification established in its application (see 21 CFR 4.102 and 314.81).

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 via the established process (see https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices#5) that includes the required information (see 21 CFR 806.10), as well as the information recommended in sections V.B.1 and V.B.5 above, within 10 working days of initiating the product removal (see 21 CFR 4.102 and 806.10).

4. Additional Considerations for this Scenario

ICSRs. If the effects on the user's eyes had been expected, a Malfunction report still would have been required but not a Fifteen-day report (see 21 CFR 4.102 and 803.50).

Correction/Removal in ICSR. If the Combination Product Applicant had initiated the removal within five working days of making the determination that a removal was necessary to prevent an unreasonable risk of substantial harm to the public health, it could have submitted a single report to satisfy both the Five-day and the correction and removal reporting requirements (see 21 CFR 4.102 and 806.10(f)).

General. Regardless of what reports an applicant has submitted to FDA for the combination product, the applicant must continue to comply with all PMSR requirements for the product. For example, in this scenario, after a Five-day report is submitted, the Applicant's requirements would include continuing to assess, and submit Fifteen-day reports as required, for adverse events (see 21 CFR 4.102(b) and 314.80).

B. Device Application Combination Product

1. Product Description and Scenario

A Combination Product Applicant holds a PMA for a drug-eluting stent (DES). The applicant receives a report that a patient experienced a life-threatening infection after the DES 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 is able to identify the product lot and reviews the production records and finds no anomalies related to any of the in-process or finished testing performed on that 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 infection was both serious (life-threatening) and unexpected (was not included in the product labeling). A Fifteen-day report (made within 30 calendar days) is required (see 21 CFR 4.102 and 314.80).

- Is the event a reportable death or serious injury?

  YES. The information reasonably suggests that DES may have caused or contributed to a life-threatening infection that required medical intervention. A serious injury report is required (see 21 CFR 4.102 and 803.50).

- 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 (see 21 CFR 4.102 and 803.50). The Combination Product Applicant submits a report within 30 calendar days that includes the required information (see 21 CFR 314.80 and 803.52,

respectively), as well as the information recommended in section 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 model of DES. 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 submits a Five-day report for the product removal that includes the information required (see 21 CFR 803.52 and 806.10) and the information recommended in section V.B above. The applicant 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 the Five-day and correction and removal reporting requirements (see 21 CFR 4.102, 803.53, and 806.10).

Non-ICSR Considerations. Because the applicant included all information required under 21 CFR 806.10 in its Five-day report, a separate correction and removal report is not required (see 21 CFR 4.102 and 806.10(f)).

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 information required under 21 CFR 314.81, as well as the information recommended in sections V.B.1 and V.B.5 above, within 3 working days of discovering the contamination issue, satisfying this additional PMSR requirement (see 21 CFR 4.102 and 314.81).

4. Additional Considerations

In this scenario, 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 (see 21 CFR 4.102 and 314.81) 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

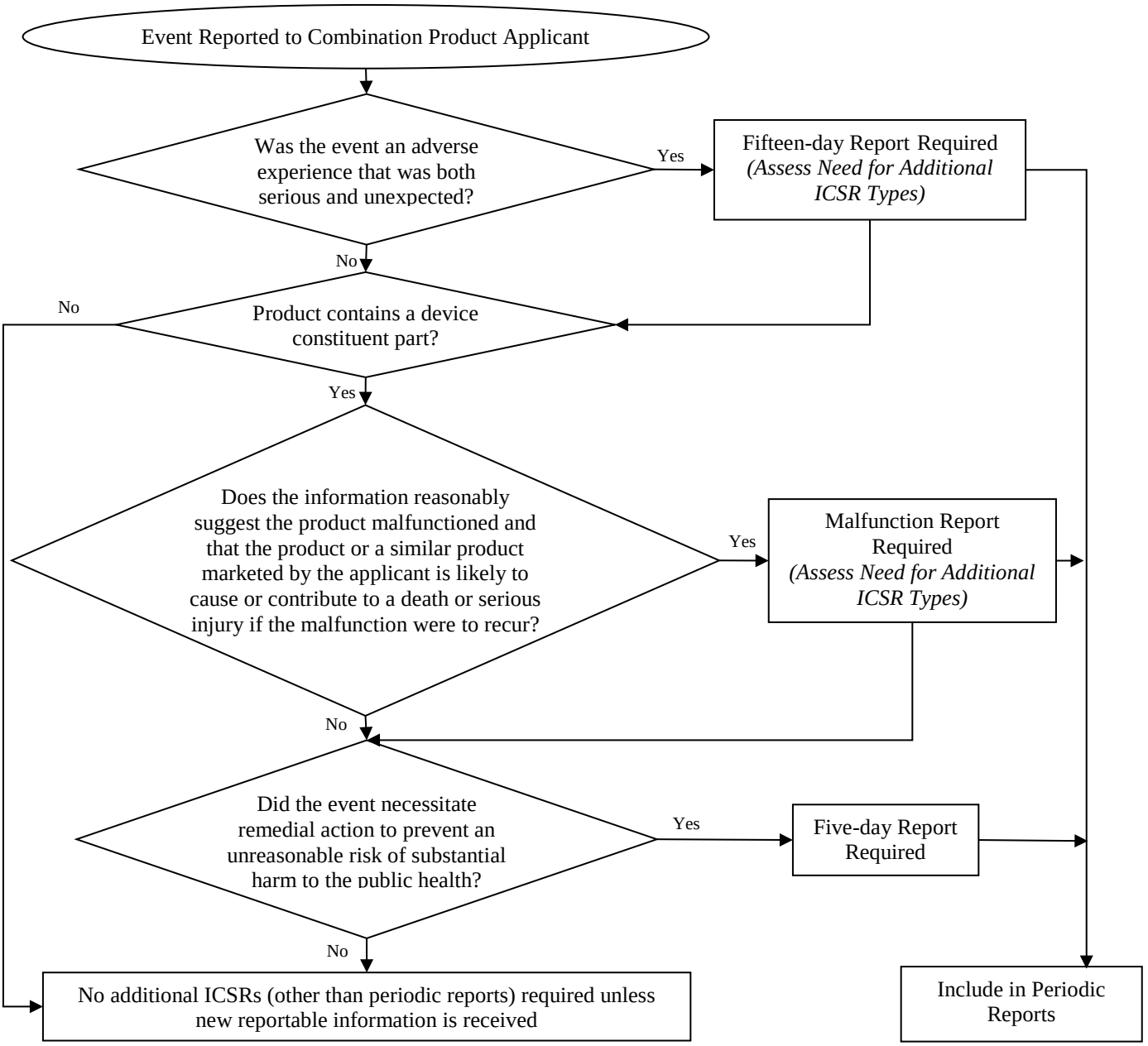
Application Type	Applicant's Product Type (CP = Combination Product)	Application Type-Based Requirements: See 21 CFR Section(s) 314	600 606	803 806	Additional Constituent Part-Based Reporting Requirements[53, 54] (see 21 CFR Section(s)): Field Alert Reports 314.81	Fifteen-day Reports 314.80	Biological 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 Applicant(s) (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 Applicant(s) (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				

[53] Note that there are associated requirements to submit follow-up reports to ICSR reports (see Section IV.A.4 for discussion of the follow-up reporting requirements in the regulations).

[54] See Sections IV.C and V.A.3 for discussion of streamlined reporting for for combination products and IV.A.1 regarding Fifteen-day reporting for combination products that contain both a drug and biological product constituent part.

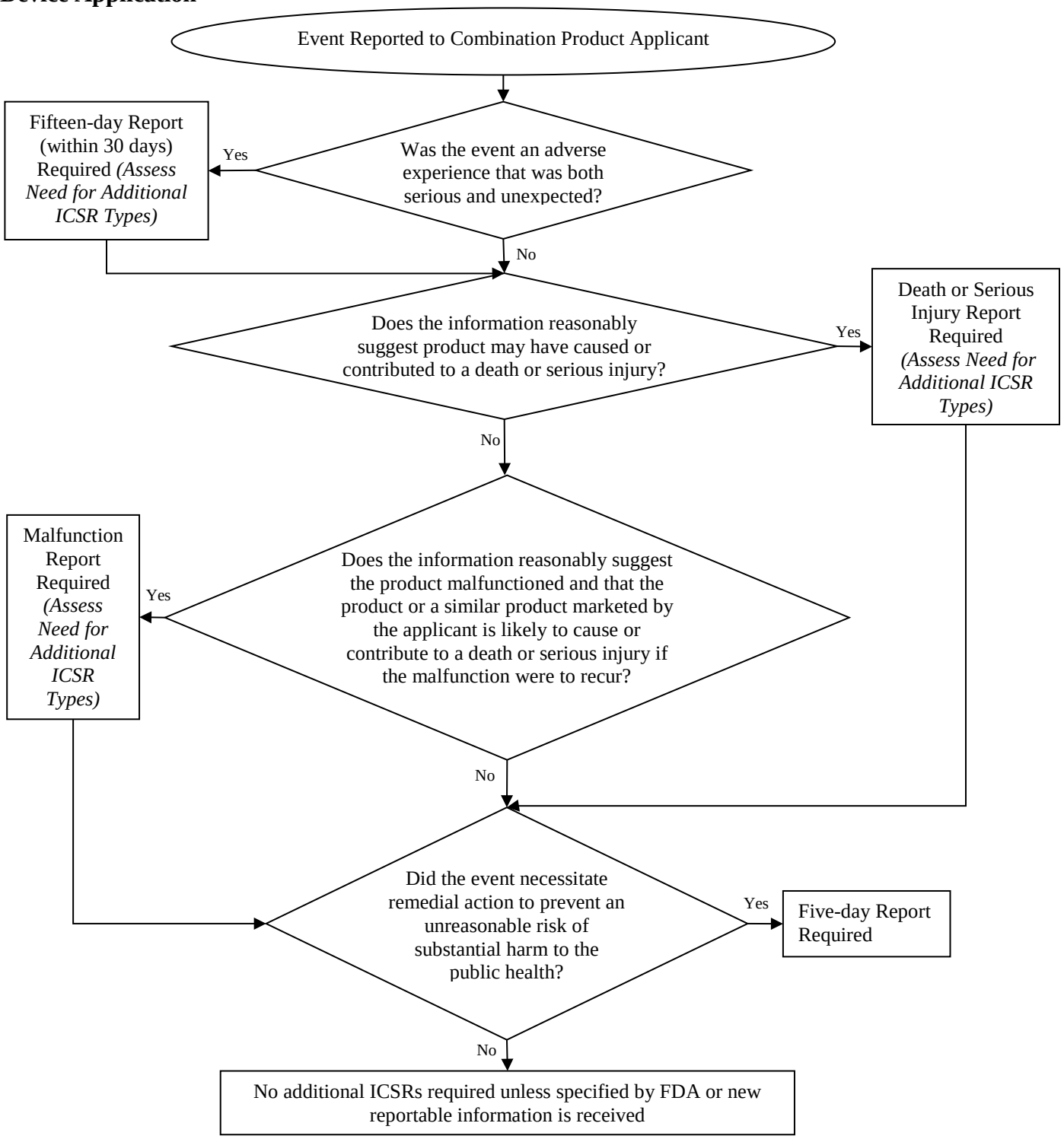
Appendix 2. Flowcharts for Combination Product ICSR Requirements

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 (21 CFR 4.101 and 4.102). Other report types (correction and removal report, FAR, BPDR) may also be required. Note options discussed in Sections IV.C and V.A.3 for streamlining by combining ICSRs and/or including correction/removal information. For ICSRs, there are associated requirements for follow-up reports (see Section IV.A.4 for discussion of follow-up reporting requirements in the regulations).

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 (21 CFR 4.101 and 4.102). Other report types (correction and removal report, FAR, BPDR) may also be required. Note options discussed in Sections IV.C and V.A.3 for streamlining by combining ICSRs and/or including correction/removal information. For ICSRs, there are associated requirements for follow-up reports (see Section IV.A.4 for discussion of follow-up reporting requirements in the regulations).

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

As discussed in Section III.A, only entities that are "Constituent Part Applicants" or "Combination Product Applicants" are subject to the combination product PSMR final rule. There are other entities, however, involved in the manufacture or marketing of a combination product that may have postmarketing safety reporting obligations for the product. Reporting obligations for such entities are indicated below:[55]

- 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.

- 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; 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 (see definitions in 21 CFR 803.3) for combination products that include a device constituent part, whether or not subject to premarket review, must comply with the requirements applicable to them 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).

- Manufacturers and importers (see definitions in 21 CFR 806.2) of combination products that include a device constituent part must comply with the requirements described in 21 CFR Part 806 for the combination product.

[55] In some cases, the constituent part of a combination product may also be manufactured or marketed separately by a different entity as a non-combination product. PMSR reporting obligations may also apply to such entities. For example, if a Combination Product Applicant purchases syringes to include in its co-packaged combination product from a syringe manufacturer who holds a marketing authorization to market the syringes for general use, the syringe manufacturer has no PMSR duties for the combination product but has PMSR duties with regard to its syringes under 21 CFR Part 803.

If you are such an entity, you should identify the product as a combination product (and you *must* identify the product as a combination product if required under the applicable regulations) 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 you. Entities who have questions about these reporting requirements should contact the lead Center or OCP, as needed.