



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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Postmarketing Safety Reporting for Combination Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is issuing regulations to set forth postmarketing safety reporting requirements for combination products. Specifically, this final rule describes the postmarketing safety reporting requirements that apply when two or more different types of regulated medical products (drugs, devices, and/or biological products, which are referred to as “constituent parts” of a combination product) comprise a combination product and the combination product or its constituent parts have received FDA marketing authorization. The rule is intended to promote and protect the public health by setting forth the requirements for postmarketing safety reporting for these combination products, and is part of FDA’s ongoing effort to ensure the consistency and appropriateness of the regulatory requirements for combination products.

DATES: *Effective date:* This rule is effective on [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

Compliance dates: Some provisions of the rule have a compliance date that is the same as the effective date of this rule, and other provisions of the rule have a later compliance date as discussed in section III.I, Effective Date and Compliance Dates.

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Executive Summary

Purpose of the Final Rule

The Agency has not previously issued regulations on postmarketing safety reporting specifically for combination products, which are products comprised of: (1) A drug and a device; (2) a device and a biological product; (3) a biological product and a drug; or (4) a drug, a device, and a biological product. Instead, the Agency has applied provisions to combination products from the postmarketing safety reporting regulations applicable to the constituent parts (i.e., reporting requirements specific to drugs, devices, and biological products). These regulations for drugs, devices, and biological products share many similarities; however, each set of regulations has certain unique reporting requirements, standards, and timeframes based in part on the characteristics of the type of product. These variations among the regulations and lack of clarity on how to apply these requirements to combination products can result in inconsistent and incomplete postmarketing safety reporting for combination products and their constituent parts.

The purpose of this final rule is to ensure consistent, complete postmarketing safety reporting requirements for combination products that have received FDA marketing authorization, while avoiding duplicative reporting. The term “postmarketing safety” is used in this rule because this rule concerns certain postmarket events, including manufacturing events, device malfunctions, and events causing injury to users, and the reporting requirements that relate to product and patient safety arising 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 once it is placed on the market.

Summary of the Major Provisions of the Final Rule

This final rule requires that a “combination product applicant” (an entity holding the application(s), as the term “application” is defined in 21 CFR 4.101 of this rule, for a combination product) and a “constituent part applicant” (an entity holding the application to market a drug, device, or biological product as a constituent part of a combination product the constituent parts of which are marketed under applications held by different applicants) comply with postmarketing safety reporting requirements applicable to the product based on the application type (e.g., new drug application, premarket approval application, biologics license application) under which the combination product or constituent part received marketing authorization. In addition to these application-type based reporting requirements, the final rule requires combination product applicants to submit additional specified reports based on the constituent parts included in the combination product (e.g., malfunction reports if the combination product includes a device, field alert reports if it includes a drug, and biological product deviation reports if it includes a biological product). The final rule requires constituent part applicants to share certain postmarketing safety information they receive with one another. The rule also specifies how combination product and constituent part applicants must submit postmarketing safety reporting information to the Agency and what records they must maintain.

The Agency received 16 sets of comments on the proposed rule. Commenters largely sought clarification of the scope of the proposed rule, how reporting requirements, timelines, and reporting standards from the underlying regulations for drugs, devices, and biological products apply, and how and what information must be shared between constituent part applicants. Several commenters, while supporting rulemaking to address postmarketing safety reporting for combination products, recommended alternative approaches. After considering the comments received on the proposed rule, the Agency has made clarifications and other revisions in the final

rule to, among other things: (1) Clarify that the final rule applies only to combination product and constituent part applicants; (2) clarify when a single report may suffice to comply with more than one reporting requirement; and (3) incorporate biological product deviation reporting and device correction and removal reporting requirements applicable to combination product applicants.

Legal Authority

The legal framework underlying this final rule is twofold. The first aspect is that drugs, devices, and biological products do not lose their discrete regulatory identities when they become constituent parts of a combination product. In general, the postmarketing safety reporting requirements specific to each constituent part of a combination product also apply to the combination product itself. Although the constituent parts of combination products retain their regulatory identities, the Federal Food, Drug, and Cosmetic Act (FD&C Act) also recognizes combination products as a category of products that are distinct from products that are solely drugs, devices, or biological products. FDA has the authority to develop regulations to ensure sufficient and appropriate ongoing assessment of the risks associated with combination products.

The second aspect of the framework is founded on the postmarketing safety reporting regulatory scheme associated with the application under which the combination product received marketing authorization, plus any applicable requirements associated with the additional six specified report types listed in this rule. Although similar in effect to the first aspect of the framework, this aspect is based on the legal authority FDA used to issue each of its existing regulations for postmarketing safety reporting for drugs, devices, and biological products.

Costs and Benefits

The final rule will generate one-time administrative costs from reading and understanding the rule, assessing current compliance, modifying existing standards of practice, changing storage and reporting software, and training personnel on the requirements under this rule. Firms that do not currently comply with the reporting requirements identified in 21 CFR 4.102(c) of this rule will also incur annual reporting costs from the submission of field alert reports, 5-day reports, 15-day reports, malfunction reports, correction or removal reports, and biological product deviation reports. The annualized total costs of the rule are between \$1.36 and \$2.68 million at a 7 percent discount rate and between \$1.35 and \$2.65 million at a 3 percent discount rate.

The final rule will benefit firms through reduced uncertainty about the reporting requirements for their specific combination product and through decreased duplicative reporting. The final rule will also benefit public health by helping to ensure that important safety information is submitted and directed to the appropriate Agency components, so that the Agency may receive and review this information in a timely manner.

I. Background

As set forth in 21 CFR Part 3, a combination product is a product comprised of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product. A combination product includes the following: (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (“single-entity” combination products); (2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (“co-packaged”

combination products); (3) 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 type of “cross-labeled” combination product); or (4) 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 the intended use, indication, or effect (another type of “cross-labeled” combination product).¹ For purposes of this rulemaking and consistent with 21 CFR 4.2, the drugs, devices, and/or biological products included in a combination product are referred to as “constituent parts” of the combination product.

A. Rationale for Rulemaking

In the proposed rule (74 FR 50744 at 50745 to 50751, October 1, 2009), FDA described its rationale and goals for the proposed rulemaking. To date, the Agency has not issued regulations on postmarketing safety reporting (PMSR) specifically for combination products. Instead, the Agency has applied provisions to combination products from the PMSR regulations applicable to the constituent parts of the combination product (i.e., the reporting requirements specific to drugs, devices, and biological products). These requirements for drugs, devices, and biological products share many similarities and have a common underlying purpose, namely to

¹ As discussed in response to Comment 1, this rule addresses only PMSR requirements for combination products that have received marketing authorization. It does not describe reporting requirements for investigational combination products.

protect the public health by ensuring a product's continued safety and effectiveness once placed on the market. However, each set of regulations has certain reporting standards and timeframes with unique requirements based in part on the characteristics of the type of product.

FDA held a public hearing on November 25, 2002, entitled "FDA Regulation of Combination Products" (Ref. 1) and a public workshop on July 8, 2003, entitled "Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges" (Ref. 2) to discuss postmarketing safety reporting, among other issues pertaining to combination products. In developing the proposed rule, we carefully considered the comments offered by stakeholders, including written comments submitted to the docket that we opened to facilitate further input on combination product issues. Two common themes from the comments were the need for consistency in postmarketing safety reporting requirements for combination products and the importance of avoiding unnecessarily duplicative reporting. Some stakeholders suggested that FDA consider developing an entirely new postmarketing safety reporting scheme for combination products, but we concluded that because of the broad similarities in the postmarketing safety reporting regulations for drugs, devices, and biological products and industry's familiarity and experience with current postmarketing safety reporting requirements, the most appropriate approach would be to rely on existing rules and to explain how to comply with them.

FDA is issuing this final rule to ensure appropriate and consistent PMSR requirements for combination products that have received FDA marketing authorization by describing how combination product applicants and constituent part applicants must comply with the PMSR regulations for drugs, devices, and biological products, and also to eliminate unnecessary PMSR requirements for such combination products.

B. The Proposed Rule

Entities subject to the proposed rule included those subject to PMSR duties under 21 CFR parts 314, 600, 606, and 803, except for user facilities and distributors as defined under part 803.

Those four sets of regulations expressly address PMSR for: (1) Drugs (part 314); (2) biological products (parts 600 and 606); and (3) devices (part 803). These sets of regulations have certain similarities. For example, the PMSR regulations for biological products, devices, and drugs each requires reports of death and other serious adverse events; each provides for expedited reporting for certain types of safety events; and each provides for followup and non-expedited reports. However, there are also certain significant differences in these sets of regulations designed, in part, to address the distinct characteristics and potential safety issues related to a particular type of product (i.e., drug, device, and biological product).

Accordingly, we proposed to require that entities comply with the PMSR requirements associated with the combination product's application type (e.g., requirements under part 314 for a combination product approved under a new drug application (NDA), or under part 803 for a combination product approved under a premarket approval application (PMA)) and also comply with certain specified additional reporting provisions that are not associated with that application type but are associated with a constituent part(s) of the combination product. The additional reporting requirements specified in the proposed rule were: (1) 5-day reports under § 803.53; (2) device malfunction reports under § 803.50; (3) 15-day "alert reports" for drugs and biological products under §§ 314.80 and 600.80; (4) field alert reports for drugs under § 314.81; and (5) expedited blood fatality reports under § 606.170. The Agency identified these five types of reports as addressing particular safety issues related to the type of article (drug, biological product, and device) and, therefore, appropriate to apply to combination products that include

that type of article regardless of the application type for the combination product, to ensure consistent and appropriate PMSR for the combination product.

The proposed rule also addressed circumstances in which the constituent parts of a combination product are marketed under separate applications, or are legally marketed by different reporters without separate applications. For constituent parts marketed under separate applications, we proposed that the reporter must comply with the reporting requirements associated with that application type. In addition, we proposed for constituent parts marketed under separate applications held by different entities or legally marketed by separate entities without an approved or cleared marketing application, that each of these entities would have a duty to share within 5 calendar days information it receives about the event, either with the other entity or entities for the combination product or with FDA. We further proposed that entities that receive postmarketing safety information from another such entity, would have to investigate the event and comply with applicable reporting obligations under the rule.

We proposed that reporters submit their reports and maintain records for them in accordance with the requirements of the underlying regulations from which the reporting duty arises (parts 314, 600, 606, or 803).

Following publication of the proposed rule, FDA participated in a workshop on January 21, 2010, entitled “Understanding Implications of the Postmarket Safety for Combination Products Proposed Rule,” sponsored by the Advanced Medical Technology Association, the Combination Products Coalition, and the Regulatory Affairs Professional Society. At this workshop, the Agency provided a summary of the proposed rule, and stakeholders then worked in groups to identify issues on which to comment.

II. Overview of the Final Rule

The final rule follows the approach presented in the proposed rule, with certain simplifications, clarifications, additions, and other changes, generally made in light of comments received, as described in sections II.A through II.F. The goal of the final rule remains the same as for the proposed rule, to ensure consistent and appropriate postmarketing safety reporting for combination products, while enabling this reporting to be as efficient as possible. Accordingly, this rulemaking seeks to apply those postmarketing safety reporting requirements to combination products necessary to ensure their safety and effectiveness, clarify how to comply with reporting requirements applicable to combination products, and enable efficiencies including submission of a single report if multiple reporting duties apply to an event. Following is a section-by-section overview of the final rule, and then a summary chart of the requirements presented in the rule.

A. Section 4.100--What is the Scope of This Subpart?

The scope of the rule remains largely the same as proposed. As in the proposed rule, § 4.100(a) reflects that the rule describes PMSR requirements for combination products. We have revised § 4.100(a) to clarify that the rule only applies to “combination product applicants” and “constituent part applicants” (as defined in §4.101); this rule does not apply to any other entities. We have also revised § 4.100(b) to clarify that the rule does not apply to investigational combination products or to combination products that have not received marketing authorization. We have eliminated proposed §4.102 as that section was largely duplicative of proposed §4.100.

B. Section 4.101--How Does FDA Define Key Terms and Phrases in This Subpart?

We eliminated unnecessary definitions, including terms not used in this final rule. We also simplified certain definitions, using cross-references to definitions provided in other provisions of Title 21 of the CFR without restating those definitions. We made these changes for

clarity and to minimize the need for amendments to this rule if a change is made in the future to the terminology or definitions in the cross-referenced provisions.²

The final rule newly includes definitions for “biological product deviation report” (BPDR) (by reference to §§ 600.14 and 606.171), and “correction or removal report” (by reference to 21 CFR 806.10), because the final rule incorporates these reporting requirements as discussed in relation to § 4.102(c) in section III.C. Similarly, we added a definition for “Product Development Protocol” (PDP) (by reference to section 515(f) of the FD&C Act (21 U.S.C. 360e(f))) and de novo classification request (by reference to section 513(f)(2) of the FD&C Act (21 U.S.C. 360c(f)(2))) because the final rule addresses these types of applications.

In addition, we included definitions for “applicant”, “combination product applicant”, “constituent part applicant”, and “device application” to help clarify which entities are subject to which duties under this rule. Specifically, we clarified that an applicant is the person holding an application under which a combination product or constituent part has received marketing authorization, and that there is a combination product applicant if there is one applicant that either holds the application for a combination product or, holds the applications for each constituent part if the constituent parts of the combination product are marketed under separate applications (as could be the case for the constituent parts of a cross-labeled combination product). We also clarified that a constituent part applicant is the applicant for a constituent part of a combination product the constituent parts of which marketed under applications held by different applicants. We defined the term “device application” to mean a PMA, PDP,

² We understand that provisions cross-referenced in this rule may be revised in the future, and we want to ensure that it is clear that those provisions as revised continue apply to combination products under this rule, without having to amend this rule each time to provide such clarity. However, if the Agency determines that a future revision to a cross-referenced provision is not appropriate to apply to combination products under this rule, or its application to combination products is unclear under this rule, we intend to amend this rule or otherwise clarify.

humanitarian device exemption (HDE), de novo classification request (request for classification under section 513(f)(2) of the FD&C Act), or premarket notification (510(k)) submission, so that we could simplify and clarify the rule by using this term to refer to all such submission types, rather than listing them each, where appropriate in the rule.

C. Section 4.102--What Reports Must you Submit to FDA for Your Combination Product or Constituent Part?

The requirements listed in § 4.102 include those that were in § 4.103 of the proposed rule with certain adjustments and additional requirements to address, in part, comments received on the proposed rule.

Specifically, we have eliminated the requirement to comply with blood fatality reporting requirements as described in § 606.170 for combination products that received marketing authorization under an application other than a biologics license application (BLA). We have also revised the requirement for all combination product applicants to submit 15-day reports as described in §§ 314.80 and 600.80, to permit these reports to be submitted within 30 days rather than 15 days for combination products that received marketing authorization under a device application.

In addition, we have incorporated BPDR and correction and removal reporting requirements for combination product applicants to ensure that the issues addressed by these reporting requirements, for biological products and devices, respectively, are also addressed for combination products that include these types of constituent parts. We have also made other adjustments in § 4.102 for clarity.

Following is a description of §4.102 as finalized, including explanations of changes from § 4.103 of the proposed rule.

1. Section 4.102(a).

A new § 4.102(a) clarifies that all applicants must comply with the applicable PMSR requirements with respect to their product. A constituent part applicant must comply with applicable requirements for the constituent part it is marketing, and a combination product applicant must comply with applicable requirements for the combination product it is marketing.

2. Section 4.102(b).

As in § 4.103(a) of the proposed rule, § 4.102(b) lists the PMSR requirements that apply based on the application type for the product. Section 4.102(b) clarifies that combination product applicants and constituent part applicants must comply with the requirements identified under § 4.102(b)(1) through (3) that are applicable based on their product's application type. In addition, § 4.102 clarifies that this rule does not require a combination product applicant to submit multiple reports relating to the same event when one report could be used to satisfy both § 4.102(b) and (c). Specifically, if the applicant has submitted one type of report and that report includes all of the information that would also be required in another type of report; is required to be submitted in the same manner under this rule as that other report; and is submitted within applicable deadlines, the submission of the single report will be considered to satisfy both reporting obligations.

The requirements of § 4.102(b) are as follows:

a. Section 4.102(b)(1). Combination product applicants and constituent part applicants must comply with the PMSR requirements under parts 803 and 806 if their product received marketing authorization under a device application.

b. Section 4.102(b)(2). Combination product applicants and constituent part applicants must comply with the PMSR requirements under part 314 if their product received marketing authorization under an NDA or abbreviated new drug application (ANDA).

c. Section 4.102(b)(3). Combination product applicants and constituent part applicants must comply with the PMSR requirements under parts 600 and 606 if their product received marketing authorization under a BLA.

3. Section 4.102(c).

This provision applies only to combination product applicants, not to constituent part applicants. It states which requirements combination product applicants must meet in addition to those associated with the product's application type, to ensure consistent and appropriate PMSR for combination products. Like § 4.102(b), it also states how applicants can submit a single report to comply with multiple reporting requirements.

As indicated previously, § 4.102(c) does not require blood fatality reporting for combination products that received marketing authorization under a device application, NDA, or ANDA, and permits combination product applicants for combination products that received marketing authorization under a device application to submit 15-day reports within 30 days rather than 15 days.

We removed the requirement under this rule to make blood fatality reports for combination products that received marketing authorization under a device application, NDA, or ANDA, because facilities at which such events occur are currently required to make blood fatality reports irrespective of the type of application under which the product received marketing authorization. Because these facilities must make such reports, we concluded that it

would be unnecessary for a combination product applicant (who is not also the operator of the facility) to report the same information as well.

In light of comments received (as discussed more fully in response to Comments 7, 8, 10), we modified the 15-day report requirement to permit these reports to be made within 30 days for combination products that received marketing authorization under a device application. We made this change based on several factors, including the following. We determined that the Agency would continue to be able to respond in a timely manner to these reports if submitted within 30 days rather than 15 days for such combination products. Further, we determined that permitting such reports to be made within 30 days would enable better alignment of reporting for device-led combination products because this timing would be consistent with the timing for submission of medical device reports. This alignment could be expected to improve the efficiency, clarity and completeness of reports for this class of combination products and to eliminate unnecessary complexity and potential for confusion.³

Section 4.102(c) includes additional reporting requirements not in the proposed rule to address specific safety concerns related to medical devices and biological products.

Combination product applicants must submit correction and removal reports as described in § 806.10 and comply with related recordkeeping requirements as described in § 806.20 for combination products that include a device constituent part; and combination product applicants

³ We considered whether to make a corresponding change for combination products that received marketing authorization under an NDA or ANDA (drug-led combination products) or under a BLA (biologic-led combination products), to require that malfunction reports be submitted within 15 days to align with the deadline for 15-day reports, in the interest of simplifying and clarifying requirements for such combination product applicants as well. However, we determined that the nature of events triggering, and the information required for, malfunction reports might make it difficult to provide a meaningful report within 15 days in some cases. As indicated in the final rule, if an event triggers both a 15-day report and a malfunction report for such a combination product, the combination product applicant can opt to comply with both reporting requirements in a single report submitted within 15 days. If the applicant determines that additional time is needed to investigate the device malfunction, the applicant can submit a followup report to the initial 15-day report with the additional information.

must submit BPDRs as described in §§ 600.14 and 606.171 for combination products that include a biological product constituent part. Having considered the unique safety issues that these additional requirements address in light of comments received, we concluded that this rule should ensure that these additional requirements are addressed by all combination product applicants for combination products that include constituent parts to which these requirements relate.

In many cases, correction and removal reporting requirements arise in relation to manufacturers' recalls in response to adverse events that may also trigger medical device reporting requirements under part 803. In such cases, submission of a medical device report (MDR) that contains all the information required by part 806 will suffice to comply with both sets of reporting requirements. Under § 806.10(f), no separate correction or removal report is required to be submitted if a report of the correction or removal has been submitted under part 803. However, in some instances, a correction or removal will not be associated with a reportable adverse event, or the action that a manufacturer takes in response will not trigger a 5-day reporting requirement, but the action must still be reported as described in part 806 to ensure, in part, appropriate coordination between the manufacturer and the Agency. In such cases, the correction or removal report currently should be submitted to the appropriate Agency field office.

Further, some corrections and removals may not trigger reporting requirements under part 803 or part 806, but may trigger recordkeeping requirements under part 806, and these recordkeeping requirements must be satisfied for combination products that include a device constituent part. Accordingly, we have incorporated the correction and removal reporting and

recordkeeping requirements under § 4.102(c) to ensure that combination product applicants comply with these requirements.

With respect to BPDRs, as discussed more fully in response to Comment 13 in section III, we concluded that these reports are akin to field alert reports for drugs, and that it was important for BPDRs to be submitted for combination products that include biological product constituent parts to enable the applicant and the Agency to address the deviation in a timely, appropriate manner. Further, we note that in most instances, a biological product deviation that is reportable under §§ 600.14 and 606.171 is not associated with an adverse experience. Accordingly, we have included in § 4.102(c) BDPR requirements for all combination product applicants whose combination products contain a biological product constituent part.

The requirements applicable to combination products applicants under § 4.102(c) are now specified as follows:

a. Section 4.102(c)(1). Combination product applicants whose combination products received marketing authorization under a BLA, NDA, or ANDA and include a device constituent part must also submit: (i) 5-day reports as described in §§ 803.3 and 803.53 and supplemental or followup reports as described in § 803.56; (ii) Malfunction reports as described in § 803.50 and supplemental or followup reports as described in § 803.56; and (iii) Correction or removal reports as described in § 806.10 and comply with recordkeeping requirements as described in § 806.20.

b. Section 4.102(c)(2). Combination product applicants whose combination products received marketing authorization under a BLA or a device application and include a drug constituent part must also submit: (i) Field alert reports as described in § 314.81 and (ii) 15-day reports and followup reports as described in § 314.80, within 30 calendar days instead of 15

calendar days if the combination product received marketing authorization under a device application.

c. Section 4.102(c)(3). Combination product applicants whose combination products received marketing authorization under an NDA, ANDA, or device application, and include a biological product constituent part must also submit: (i) BPDRs as described in §§ 600.14 and 606.171 and (ii) 15-day reports and followup reports as described in § 600.80, within 30 calendar days instead of 15 calendar days if the combination product received marketing authorization under a device application.

4. Section 4.102(d).

This provision replaces and has been revised as compared to proposed § 4.103(c) to: (a) clarify that it applies only to combination product applicants; (b) identify the content expected in periodic safety reports for combination products that received marketing authorization under an NDA, ANDA, or BLA; and (c) provide that additional reporting is required for combination products that received marketing authorization under a device application only upon notification by the Agency if the Agency determines additional or clarifying safety information is required to protect the public health. Section 4.102(d) has two paragraphs stating the following requirements:

a. Section 4.102(d)(1). Combination product applicants for combination products that received marketing authorization under an NDA, ANDA, or BLA must include in their periodic safety reports, in addition to information required under § 314.80 or 600.80, respectively, a summary and analysis of reports that the applicant submitted in accordance with § 4.102(c)(1)(i) and/or (ii) (5-day and malfunction reporting requirements).

b. Section 4.102(d)(2). Combination product applicants for combination products that received marketing authorization under a device application do not have to make periodic reports under this rule but must submit additional reports regarding postmarketing safety events in accordance with written requests by the Agency that will be made only if the Agency determines that protection of the public health requires additional or clarifying safety information. Any such written request will specify the safety information to include in such reports and the reason or purpose for the request.

D. Section 4.103--What Information Must You Share with Other Constituent Part Applicants for the Combination Product?

As discussed more fully in response to Comment 18 in section III, the final rule makes clear that the duties to share information within 5 calendar days under § 4.103 (replacing § 4.104 in the proposed rule) apply only to constituent part applicants. In addition, we clarified and simplified these requirements. Constituent part applicants must share only information they receive regarding events that involve a death or serious injury within the meaning of § 803.3 or an adverse experience within the meaning of § 314.80(a) or § 600.80(a), and must share this information only with each other; we have eliminated the alternative of sharing the information with FDA as unnecessary and inefficient. Also, we have removed as unnecessary the content of proposed § 4.104(b) regarding how to respond to information received from another constituent part applicant. Section 4.102(b) states which PMSR requirements apply to constituent part applicants, and those PMSR requirements prescribe under what circumstances an entity subject to them must submit a report regarding information that the entity receives.

We have added a new § 4.103(b) addressing recordkeeping for this information sharing duty. This provision has been added to provide constituent part applicants appropriate clarity

and certainty regarding what records to keep and what documentation the Agency will consider adequate to demonstrate compliance with the information-sharing requirement.

E. Section 4.104--How and Where Must You Submit Postmarketing Safety Reports for Your Combination Product or Constituent Part?

This section has been revised as compared to proposed § 4.105, to clarify where and how to submit postmarketing safety reports for constituent part applicants (§ 4.104(a)) and combination product applicants (§ 4.104(b)).

1. Section 4.104(a).

Constituent part applicants must make all reports in accordance with the existing regulations applicable to that type of product (for example, making reports in accordance with the requirements of part 314 if the constituent part is a drug). Like an applicant for a non-combination product, a constituent part applicant holds an application for a single type of article (drug, device, or biological product) and is required to make postmarketing safety reports to FDA only for events concerning its product. Accordingly, these reports are most appropriately submitted to the same Agency components in the same manner as they would be by any applicant holding an application for the same type of product.

2. Section 4.104(b).

Combination product applicants are required to submit postmarketing safety reports concerning the combination product, including each of that combination product's constituent parts. The nature of the events and the appropriate Agency component to contact regarding them can vary however. In light of these considerations, § 4.104(b) draws a distinction between

individual case study reports (ICSRs) (Ref. 3) for safety events experienced by individual users of combination products⁴ and other safety reports.

Section 4.104(b) requires that combination product applicants must submit all ICSRs (15-day reports, malfunction reports, serious injury or death reports, and 5-day reports) applicable to the combination product in the manner specified in the PMSR regulations associated with the application type for the combination product. See §§ 4.104(b)(1) and (2).

This approach to submission of ICSRs by combination product applicants best assures the clarity, completeness, and efficiency of such reporting. Having all ICSRs submitted in the same manner to the Center with the lead for the application enables multiple reporting requirements for an event to be satisfied by submitting a single report and ensures that all such reports relating to the same event will be captured in a single series (see also response to Comment 24).

In addition, under § 4.104(b), all BPDRs, field alert reports, and correction and removal reports must be submitted as described in the regulations from which these reporting requirements arise. The Agency currently receives these reports through differing mechanisms and Agency components based on such factors as logistical considerations and expertise to take the lead in assessing and addressing the issues raised in the report. For example, field alert reports for drugs currently must be submitted to FDA district offices as described in part 314, and BPDRs currently must be submitted to the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER) as appropriate based on which of these two Centers would ordinarily have jurisdiction over the type of biological product

⁴ “Individual case study report” or ICSR is the internationally recognized term of art referring to reports of an adverse event, including a malfunction, experienced by an individual user of the product. This term is used to refer to such reports in international standards, and FDA implementing materials, regarding proper methods for submitting ICSRs to regulatory bodies for drugs, biologics, and devices.

included in the combination product, as described in parts 600 and 606. These existing reporting systems are designed to assure timely, effective resolution of the matters raised in these reports.

As discussed in response to Comment 28 and in section III.A., the Agency anticipates issuing a guidance to provide recommendations on how applicants may adopt more streamlined, effective approaches to making reports under this rule.

F. Section 4.105--What are the Postmarketing Safety Reporting Recordkeeping Requirements for Your Combination Product or Constituent Part?

As discussed more fully in section III, response to Comment 26, we revised this section (replacing § 4.106 in the proposed rule) to clarify and simplify the recordkeeping requirements associated with PMSR obligations for combination product applicants and constituent part applicants. Section 4.105(a) describes the recordkeeping requirements for constituent part applicants and § 4.105(b) describes the requirements for combination product applicants, as follows:

1. Section 4.105(a).

Constituent part applicants must comply with the recordkeeping requirements prescribed in the underlying PMSR regulations identified in § 4.102(b) as applicable to the product based on its application type. In addition, they must retain the records required in § 4.103 (information sharing) for the longest retention period (if more than one period applies) required for records under the PMSR regulations applicable to their constituent part (as explained in response to Comment 26).

2. Section 4.105(b).

Combination product applicants must maintain records relating to their postmarketing safety reports for whichever is the longest required record-keeping period under the PMSR

requirements applicable to the combination product applicant under § 4.102. Because both parts 314 and 600 currently require recordkeeping for 10 years, at this time the recordkeeping period for combination product applicant PMSR records would be at least 10 years.

Table 1.--Requirements for BOTH Constituent Part Applicants and Combination Product Applicants¹ (See § 4.102(b) of this rule)

Source of PMSR Requirements	Application Types		
	ANDA/NDA	BLA	Device Application
Part 314	X		
Part 600			X
Part 606			X
Part 803			X
Part 806			X

¹ In addition to the requirements in table 1, constituent part applicants must share certain adverse event information with other constituent part applicant(s) for the combination product. (See § 4.103 of this rule).

Table 2.--Additional Requirements ONLY for Combination Product Applicants¹ (See § 4.102(c) of this rule)

Combination Product Includes	Reporting Requirement	Application Type		
		ANDA/NDA	BLA	Device Application
Drug	§ 314.81, Field Alert Reports	See table 1	X	X
	§ 314.80, 15-Day Reports (initial and followup)		X	X
Biologic	§§ 600.14 and 606.171, Biological Product Deviation Reports	X	See table 1	X
	§ 600.80, 15-day Reports (initial and followup)	X		X
Device	§§ 803.53 and 803.56, 5-Day Reports (initial and supplemental or followup)	X	X	See table 1
	§§ 803.50 and 803.56, Malfunction Reports (initial and supplemental or followup)	X	X	
	Part 806, Correction or Removal Reports and Records	X	X	

¹ In addition to the requirements in table 2, the rule addresses other reporting requirements for combination product applicants as follows: (1) Combination products that received marketing authorization under an NDA, ANDA, or BLA: Include a summary and analysis of malfunction (§§ 803.50 and 803.56) and 5-day (§§ 803.53 and 803.56) reports submitted during the report interval in the periodic safety reports (see § 4.102(d)(1)) and (2) combination products that received marketing authorization under a device application: Submit additional reports when notified by the Agency because FDA has determined the information is required to protect the public health (see § 4.102(d)(2)).

III. Comments on the Proposed Rule

We received comments from 15 entities and one individual on the proposed rule.

Commenters included trade organizations and manufacturers of drugs, devices, biological

products, and combination products. Many commenters sought clarification on particular points or recommended adjustments to specific aspects of the proposed rule. Several commenters, while supporting rulemaking to address PMSR for combination products, recommended alternative approaches as discussed in Comment 27.

To make it easier to identify comments and our responses, the word “Comment” appears before the descriptions of the comments, and the word “Response” appears before our response. We have also numbered comments to help distinguish among them. The number assigned to each comment is purely for organizational purposes and does not signify relative value or importance of comments or the order in which they were received. Certain comments are grouped together under a single number because the subject matter of the comments was similar.

A. Section 4.100--What is the Scope of This Subpart?

(Comment 1) Some commenters sought clarification of safety reporting requirements for investigational combination products through guidance or expansion of the scope of the rule, including for investigational combination products that contain a legally marketed article as a constituent part. One commenter asked if the Agency is planning to publish guidance on this issue. One commenter asked that the Agency clearly lay out the responsibilities of the manufacturer of an approved product in the investigational setting.

(Response1) Safety reporting for investigational products is an important issue for combination products, just as it is for drugs, devices, and biological products. However, this rule only discusses the PMSR requirements for combination products that have received marketing authorization. As stated in § 4.100(b), this rule does not apply to investigational combination products. The safety reporting requirements for investigational new drugs are in 21 CFR 312.32, and the safety reporting requirements for investigational devices are in 21 CFR 812.150. The

Agency intends to continue developing guidance relating to this topic for combination products. If you have questions regarding how to comply with the reporting requirements for your investigational combination product, please raise them with the review division in CDER, CBER, or the Center for Devices and Radiological Health (CDRH) that is responsible for reviewing your application, or with the Office of Combination Products (OCP) as needed.

(Comment 2) Some commenters requested that the Agency clarify which entities and products are subject to this rule. Some commenters proposed clarifying that this rule applies only to application holders. Other commenters sought clarification of the rule's applicability to devices marketed under a 510(k) clearance and to non-applicants, including contract manufacturers. One commenter asked for clarification of whether the rule would apply to component suppliers. One commenter sought clarification of which entities have reporting requirements under this rule for combination products composed of constituent parts marketed under separate applications. One commenter proposed that the Agency prepare a comprehensive list of products by class, product code or other designations that are subject to this rule.

(Response 2). As also discussed in section II (discussions of §§ 4.100 and 4.101), in light of comments received, we have amended this rule to clarify which entities it addresses and what PMSR requirements apply to them. We have clarified that this rule applies only to "combination product applicants" and "constituent part applicants," as those terms are defined in § 4.101. We also have clarified the final rule to state which requirements apply to combination product applicants and which apply to constituent part applicants.

Under § 4.101 of this rule, the term "applicant" is defined to mean a person holding an application (BLA, NDA, ANDA, PMA, HDE, PDP, de novo classification request or premarket notification (510(k)) submission) under which a combination product or constituent part has

received marketing authorization (see also definitions for “application” and “device application”); “combination product” is defined to mean a product meeting the definition for this term under § 3.2(e); and the term “constituent part” is defined as in § 4.2 to mean a drug, device, or biological product that is part of a combination product. The term “combination product applicant” is defined to mean an applicant holding the application(s) for a combination product (i.e., either holding the application for the entire combination product or the applications for each constituent part--in some cases the constituent parts of a combination product are marketed under their own marketing authorizations, as might be the case for a cross-labeled combination product for example), and “constituent part applicant” is defined to mean an applicant for a constituent part of a combination product the constituent parts of which are marketed under applications held by different applicants. In other words, if a single entity holds the application (s) under which a combination product is marketed, that entity is the combination product applicant; there are no constituent part applicants for that combination product. If instead, one applicant receives marketing authorization to market a constituent part of a combination product and another applicant receives marketing authorization to market another constituent part of that combination product, each of those entities is a constituent part applicant for their constituent part of that combination product. Importers, component manufacturers and suppliers, and any other entities that do not meet the definition of combination product applicant or constituent part applicant, are not subject to this rule.⁵

⁵ We note that all entities that are not subject to this rule but that have reporting requirements under other regulations must comply with those requirements, including, as appropriate, with respect to events relating to a combination product. For example, although they are not applicants under this rule, entities marketing unapproved combination products must comply with all applicable PMSR requirements, for instance under 21 CFR Part 310, for their products. Similarly, all entities subject to PMSR requirements under parts 314, 600, 606, 803, and 806 must comply with those requirements including for events relating to a combination product.

We note that non-applicants subject to reporting requirements under 314.80 and 600.80 may provide their reports to the applicant rather than the Agency. Similarly, non-applicants subject to reporting requirements under

To illustrate how these definitions are used to determine who is subject to this rule, take the example of a prefilled syringe that received marketing authorization under an NDA or ANDA held by entity A, which purchases the syringe components for this product from entity B, which manufactures the syringe components. Entity A is the only applicant for the combination product, and, therefore, is the combination product applicant and must comply with the provisions of this rule applicable to combination product applicants. There are no constituent part applicants for the combination product. Entity B has no reporting duties under this rule (nor does it have any under part 803 or 806 for the syringe components⁶). (It bears noting that entity A is responsible not only for reporting but also for conducting any necessary quality investigations for the combination product as a whole and may need to coordinate with entity B for such investigations and to address safety issues relating to the device constituent part for the combination product.) If entity B were also to manufacture and separately market under a 510(k) complete, finished, empty syringes, not as part of a combination product, entity B would be subject to reporting requirements under parts 803 and 806, but would not be subject to this rule for this device. Entity A would remain the sole applicant for the combination product, i.e., the combination product applicant. Similarly, if entity B manufactured syringes to supply to entity A for inclusion in kits for which entity A received marketing authorization under an NDA or ANDA, entity A would still be the sole applicant for the combination product, i.e., the

part 803 may request a reporting exemption from CDRH under § 803.19. Accordingly, entities that are not combination product applicants or constituent part applicants, as those terms are defined under this rule (importers, for example), who have reporting duties under part 803 in relation to a combination product may request a reporting exemption, subject to § 803.19. We intend to provide further information on these topics for combination products in guidance.

⁶ Parts 803 and 806 apply to, among others, device “manufacturers,” and under §§ 803.3 and 806.2, device “manufacturers” include entities that manufacture components which are devices that are ready to be used and are intended to be commercially distributed and intended to be used as is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient.

combination product applicant, since it holds the NDA or ANDA under which the kits received marketing authorization, and, therefore, only entity A would be subject to this rule.

To take another example, if entity C receives marketing authorization under a PMA or 510(k) to market an imaging device as a constituent part of a cross-labeled combination product, and entity D receives marketing authorization under an NDA or ANDA to market a contrast agent drug as a constituent part of that same cross-labeled combination product, then entities C and D are both constituent part applicants, and both are subject to the provisions of this rule applicable to constituent part applicants. There is no combination product applicant for this product.

Regarding one commenter's request for the Agency to develop a comprehensive list of products subject to this rule, we note that combination products are marketed for diverse medical purposes and include a wide variety of constituent parts, making a comprehensive listing impractical to compile. The definition of combination product is provided at § 3.2(e), and additional information regarding product classification is available on the Web page for OCP. In addition, regulated entities may seek feedback from OCP regarding the classification of their products, including by submitting a request for designation (RFD) in accordance with part 3 to obtain a formal decision from the Agency of whether their product is a drug, device, biological product, or combination product. Guidance for how to prepare an RFD is available on OCP's Web page (<http://www.fda.gov/CombinationProducts/default.htm>).

B. Section 4.101--How Does FDA Define Key Terms and Phrases in this Subpart?

(Comment 3) One commenter thought we should clarify what we mean by "combination product," and in particular whether we mean to include products that combine only two or more of the same type of article, such as a drug and a drug.

(Response 3) This rule defines combination products as those products falling within the scope of § 3.2(e). Under § 3.2(e), a combination product must include: A drug and either a device or biological product; a device and either a drug or biological product; a biological product and either a drug or device; or a drug, device, and a biological product. A product that includes only multiple drugs, multiple devices, or multiple biological products is not a combination product as defined in § 3.2(e).

(Comment 4) Some commenters proposed that we clarify what products fall within the scope of “cross-labeled” combination products as described in § 3.2(e)(3), with some noting that the preamble to the part 3 regulation (56 FR 58754, November 21, 1991) states that most drugs, devices, and biological products intended for concomitant use are not combination products. One commenter stated that the Agency must issue “guidance on cross-labeled combination products” before the effective date of this rule “for meaningful implementation of this rule.”

(Response 4) While we disagree that we must issue guidance on cross-labeled combination products prior to the effective date for this final rule, we agree that clarifying when separately distributed articles constitute a combination product would be helpful. This issue may be relevant not only for purposes of postmarketing safety reporting, but to all aspects of the regulation of such combination products. Whether a drug, device, and/or biological product together constitute a cross-labeled combination product generally would be determined during the premarket review process, but sponsors may, for example, wish to clarify the matter earlier in product development. If sponsors have questions regarding whether a drug, device, and/or biological product that are intended to be separately distributed, but intended to be used with one another constitute a cross-labeled combination product, we encourage them to contact OCP. If

sponsors wish to obtain a formal classification determination from the Agency, they may submit an RFD to OCP (see Comment 2).

FDA intends to publish a guidance that provides recommendations on how to comply with the requirements under this rule for combination products, including cross-labeled combination products.

(Comment 5) Two commenters noted that the definition of “constituent part” incorrectly cited § 3.1(e), a non-existent provision, rather than § 3.2(e), which is the citation for the “combination product” definition.

(Response 5) We have corrected this error by revising the definition to cite to § 4.2 as “constituent part” is defined in that section.

(Comment 6) Some commenters expressed concerns regarding the definition of “constituent part” for this rule and asked how constituent parts of combination products compare to components of devices. Some commenters specifically raised concerns that the definition of constituent part would result in certain entities, which are currently not subject to reporting requirements, becoming subject to PMSR requirements under this rule. Some commenters proposed revising the definition for “constituent part” and adding a definition for “component” in this rule to clarify that components of drugs, devices, and biological products are not constituent parts.

(Response 6) The purpose of the term “constituent part” is to identify the drug, device, and/or biological products that are part of a combination product. We believe the questions and concerns raised in these comments are fully addressed by the revisions we have made to the rule. As discussed in sections II.A and B (discussions of §§ 4.100 and 4.101) and in response to

Comment 2, we have included definitions of “combination product applicant” and “constituent part applicant,” and clarified that this rule applies only to these two categories of entities.

The term “component” is defined elsewhere in Title 21 for drugs and devices (see 21 CFR Parts 210, 212, and 820). Because the term “component” is not used in this rule, we determined it is not necessary to define the term as part of this rulemaking.

C. Section 4.102--What Reports Must You Submit to FDA for Your Combination Product or Constituent Part?

(Comment 7) Several commenters requested that the Agency clarify under what circumstances this rule might require the submission of multiple reports in relation to the same event. In this regard, some commenters sought clarification of what reports “supersede” others and under what circumstances the submission of one type of report applicable to a combination product would obviate the need to submit a second type of report for the same event. Another commenter sought clarification of reporting requirements for combination products comprised of constituent parts marketed under separate constituent part applications.

(Response 7) Under this rule, combination product applicants and constituent part applicants must submit reports as required by the PMSR requirements applicable to that applicant under § 4.102. Constituent part applicants are subject to only one set of PMSR requirements under this rule (in addition to the duty to share information with other constituent part applicants for the combination product, in accordance with § 4.103 as discussed in section II.D). Specifically, constituent part applicants must comply only with the PMSR requirements listed under § 4.102(b) based on the application type for their constituent part (e.g., parts 803 and 806 PMSR requirements if the constituent part received marketing authorization under a device application). Combination product applicants also must comply with the PMSR requirements

applicable to their combination product under § 4.102(b) based on the application type for their combination product. In addition, combination product applicants must comply with the PMSR requirements identified in § 4.102(c) as applicable based on the types of constituent parts (drug, device, and/or biological product) that the combination product includes.

We have clarified when a single report may suffice to comply with more than one reporting requirement for combination product applicants.⁷ If a combination product applicant submits a report that satisfies multiple applicable reporting requirements, including all submission deadlines, for reports required to be submitted in the same manner, then the applicant does not need to submit any additional reports to satisfy those reporting requirements. As an example, a combination product applicant who holds an NDA for a drug-device combination product must submit both 15-day reports as described in § 314.80 and malfunction reports as described in § 803.50, for an event that triggers both duties. That applicant could satisfy both requirements by submitting a single report within 15 days that includes all of the information that would be required in both types of reports for the event.

(Comment 8) Some commenters sought clarification of the standards for submitting a report under this rule. One commenter requested clarification of whether limitations established under §§ 314.80 and 600.80 for 15-day reporting requirements with respect to postmarketing studies apply to combination products under this rule. Other commenters sought clarification of the standard for when to submit an expedited report under § 314.80 or § 600.80, which state that events must be reported if “associated with” the use of the product, “whether or not considered”

⁷ Constituent part applicants are subject only to the PMSR regulations applicable to their type of constituent part (drug, device, or biological product) (in addition to the duty to share information with other constituent part applicants for the combination product, in accordance with § 4.103 of this rule, as discussed elsewhere in this preamble). Accordingly, any circumstances under which they may be able to comply with more than one reporting requirement through a single report are identified in those PMSR regulations (see, e.g., § 806.10(f)).

drug or biologic related. Other commenters requested clarification of how to interpret aspects of the device reporting standards in part 803, such as the meaning of “reasonably suggests” in relation to whether the event is reportable, the meaning of “unreasonable risk of substantial harm to the public health” in relation to 5-day reports, and the meaning of “caused or contributed,” a term defined under § 803.3.

(Response 8) The standards in this rule for when to submit a report are those established in the underlying PMSR regulations listed in §4.102(b) and (c), including any exceptions provided in those underlying regulations. The standards and definitions for the underlying PMSR requirements, such as the definition of “caused or contributed” in § 803.3, remain applicable for combination products and their constituent parts.

For instance, if you are a combination product applicant for a drug-device combination product, in deciding whether you must submit a 15-day report for a serious, unlabeled adverse event, you must determine if the event was “associated with” the use of the combination product, and if so, you must submit the report regardless of whether you believe the combination product caused or contributed to the event. Similarly, in deciding whether you must submit a malfunction report, you must assess, among other things, whether the information “reasonably suggests” that the product malfunctioned. If the information does not “reasonably suggest” that a malfunction occurred, then a malfunction report would not be required.

If you are a combination product applicant and your combination product received marketing authorization under a device application, in deciding whether you must submit a serious injury or death report, you must consider whether the information “reasonably suggests” that the combination product may have caused or contributed to the death or serious injury in

which case you must submit a report even if the event does not trigger submittal of a 15-day report.

In some cases, a report required under § 4.102(c) for a combination product applicant may address a constituent part; in others, it may address the combination product as a whole. For example, correction or removal that triggers a correction or removal report may involve the entire combination product. Bacteriological contamination or a significant change or deterioration to the drug constituent part that triggers a field alert report may relate to an aspect of manufacturing for the drug alone, or may also relate to an aspect of the manufacture of the combination product as a whole that is affecting the drug constituent part. A manufacturing deviation or other event that may affect the safety, purity, or potency of a biological product constituent part and trigger a BPDR may involve the biological product alone, or the combination product as a whole. In all cases, the report should fully present the issues, including with respect to each constituent part and the combination product as a whole, as applicable, to ensure an appropriate response to the event.

(Comment 9) One commenter sought clarification of what adverse events would be considered “unexpected,” for purposes of §§ 314.80 and 600.80 with regard to combination products. Another commenter asked whether a serious adverse event that is expected under the drug labeling for a combination product and that does not involve a device malfunction should be reported in an expedited manner. In relation to these issues, other commenters also raised whether this rule will “require labeling specific to the combination product,” and whether a distinct understanding of “expectedness” would need to be developed with respect to combination products marketed under a device application as opposed to an NDA or BLA due to differences in product review and labeling.

(Response 9) Under this rule, a serious adverse event could trigger a requirement for submission of a 15-day report as described in § 314.80 or § 600.80 by a combination product applicant or a drug or biological product constituent part applicant if the event is not listed in the current FDA-approved labeling for the combination product.

While this rule does not establish any labeling requirements, we recognize that there is a question of what labeling is relevant to a determination of whether an adverse event is unexpected for purposes of 15-day reports described in §§ 314.80 and 600.80, if the constituent parts of the combination product have their own labeling.

Our goal is to ensure timely, complete reporting without creating unnecessary redundancy of reporting. Combination product labeling must meet the labeling requirements for each constituent part, including all required information regarding the risks associated with the use of the combination product. The term “expectedness” for purposes of § 314.80 or § 600.80 should be interpreted in the same manner regardless of the type of application(s) under which the combination product received marketing authorization.

Accordingly, in determining whether an adverse experience is unexpected, it is appropriate to consider all of the FDA-approved labeling for the combination product. For example, if the constituent parts of a cross-labeled combination product have their own labeling, and the event is addressed in the labeling for either constituent part, the event is expected for the combination product.

(Comment 10) One commenter proposed that the requirements for submitting postmarketing 15-day reports and MDRs be consolidated for combination products, arguing that this would eliminate duplicative reporting as much as possible and improve efficiency. Other

commenters proposed applying only the reporting requirements associated with the application type if it is unclear which constituent part or parts contributed to the event.

(Response 10) We agree with the goal of consolidating requirements and avoiding unnecessary redundancy in reporting for combination products. To this end, we have not required submission of serious injury and death reports under part 803 for combination products that received marketing authorization under a BLA, NDA, or ANDA and that include a device constituent part, based on the premise that the requirements of §§ 600.80 and 314.80, respectively, ensure timely reporting of such events for such combination products. In addition, as discussed in section II.C, discussion of § 4.102(c), we have revised the requirement for combination product applicants to submit 15-day reports to permit these reports to be submitted within 30 days for combination products that received marketing authorization under a device application, so that the timing for these reports corresponds to the timing for related MDRs for such combination products, specifically serious injury, death, and malfunction reports. Further, we have clarified that applicants need not submit multiple types of reports for the same event if they are able to satisfy the requirements of each in a single report.

As discussed in the preamble to the proposed rule, there are certain significant differences in the PMSR regulations for drugs, devices, and biological products, that address distinct characteristics and potential safety issues associated with the particular type of product, and the public health benefit of these unique provisions would be lost if the combination product were subject solely to the reporting requirements associated with the application type (74 FR 50744 at 50746). For example, malfunction reports can address distinct issues that are not captured by other reporting requirements and need to be submitted for all combination products that include a device constituent part. Specifically, malfunction reports ensure that the Agency receives notice

of malfunctions of combination products and device constituent parts if that product or a similar one marketed by that applicant would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

(Comment 11) One commenter argued that the proposed rule included provisions that could result in inconsistent reporting requirements. This commenter stated that an applicant for a drug-device combination product marketed under a single application would have a duty to address adverse events caused by the device under 15-day reporting requirements while, if a drug-device combination product were marketed under separate applications for the drug and device, the 15-day reporting requirements would extend only to the adverse events caused by the drug.

(Response 11) This final rule clarifies these reporting requirements, which we do not consider to be inconsistent. As the commenter indicates, 15-day reports are required for combination product applicants and for drug and biological product constituent part applicants. The scope of these reporting requirements depends on the type of product (drug, biological product, device, combination product) that is marketed by the applicant. A combination product applicant must report unexpected serious adverse events associated with its product, i.e., the combination product. A drug or biological product constituent part applicant must report unexpected serious adverse events associated with its product, i.e., the drug or biological product, and also must share information it receives with the other constituent part applicant(s) for that combination product in accordance with § 4.103. The other constituent part applicant(s) then must comply with any applicable PMSR requirements for its product with respect to that event, including preparation and submission of reports as appropriate.

(Comment 12) One commenter sought clarification of when the clock starts for a 5-day report (as described in §§ 803.3 and 803.53).

(Response 12) This rule does not affect or change when the clock starts for reporting requirements. The clock starts for a 5-day report for a combination product as it would for a device. As required under § 803.53(a), the clock begins when you become aware that a reportable event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. Or, as required under § 803.53(b), the clock begins when you receive a written request from FDA for the submission of a 5-day report. Additional information on the timing requirements associated with 5-day reports is in the CDRH guidance document “Medical Device Reporting for Manufacturers” available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm359566.pdf>.

(Comment 13) One commenter proposed BPDRs as an additional type of required report to include among the specified required reports listed in proposed § 4.103(b), arguing that BPDRs serve a purpose similar to field alert reports and, therefore, would be appropriate to include as well.

(Response 13) We agree with this comment. To ensure the completeness of postmarketing safety reports for combination products that include a biological product constituent part, including combination products that received marketing authorization under an NDA, ANDA, or device application, we are explicitly including BPDRs under § 4.102(c). Similar to field alert reports for drugs, BPDRs address events associated with manufacturing that represent a deviation from current good manufacturing practice, applicable regulations, applicable standards or established specifications, or represent an unexpected or unforeseeable

event that may affect the safety, purity, or potency of the product. Therefore, we are adding BPDRs to the list of types of reports under § 4.102(c) that a combination product applicant must submit if the combination product includes a biological product constituent part.

(Comment 14) One commenter sought clarification of the application of part 806 device correction and removal reporting requirements within the proposed PMSR system for combination products. The commenter also sought confirmation that part 806 reporting requirements can be met for combination products through part 803 reporting, as they can for devices that are not constituent parts of combination products.

(Response 14) To address this comment, we have expressly incorporated under § 4.102(c) correction and removal reporting described in § 806.10 and associated recordkeeping requirements described in § 806.20. We have made this change to provide clarity, promote efficiency, and ensure the completeness of postmarketing safety reports for combination products that include a device constituent part.

Part 806 implements, in part, section 519(g) of the FD&C Act (21 U.S.C. 360i), which was enacted due to Congressional concern that device manufacturers were carrying out product corrections or removals without notifying FDA or not doing so in a timely fashion (H.R. Rep. No. 101-808, at 29 (1990); S. Rep. No. 101-513, at 23 (1990)). Congress explained that industry's failure to report corrections and removals, particularly those undertaken to reduce risks associated with the use of a device, "denies the agency the opportunity to fulfill its public health responsibilities by evaluating device-related problems and the adequacy of corrective actions" (S. Rep. No. 101-513, at 23), and "has seriously interfered with the FDA's ability to take prompt action against potentially dangerous devices" (H. R. Rep. No. 101-808, at 29).

FDA believes that correction and removal reporting and recordkeeping for combination products containing a device constituent part is necessary to protect the public health as envisioned by Congress, by ensuring that the Agency has current and complete information regarding those actions taken by applicants to reduce risks to health caused by their products. Reports of such actions will improve the Agency's ability to evaluate problems and to take prompt action against potentially dangerous combination products, regardless of the type of application under which the combination product received marketing authorization.

As for all of the PMSR requirements incorporated into this rule by reference, the standards for how to report under § 806.10 and for recordkeeping under § 806.20 are not affected by this rule, including not having to submit an 806 report if the correction or removal is addressed in a report submitted under part 803 (§ 806.10(f)). To enable efficient reporting and avoid unnecessarily redundant reports, this rule provides that part 803 reporting requirements can be satisfied through submission of drug or biological product reports, as explained in response to comment 7. Similarly, part 806 reporting requirements also can be satisfied through submission of an MDR or 15-day report, so long as the report includes all of the information needed to comply with the requirements of part 806 and is filed within 10 working days of initiating the correction or removal, as described in § 806.10.

In circumstances in which a 15-day report or MDR is not triggered but reporting under part 806 is required, reports of corrections or removals should be sent to the FDA in the same manner as for other such reports unless otherwise specified by the Agency. Currently, reports required under part 806 are submitted to the district office for the district in which the reporting facility is located, on the basis that the district office can best monitor the firm's removal or corrections activities in a timely fashion. Combination product applicants for combination

products with a device constituent part who initiate a correction or removal that is not required to be reported to FDA under 806.10, must maintain a record of the correction or removal as described in § 806.20.

(Comment 15) Some commenters sought clarification of the applicability of section 227 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) concerning the reporting of malfunctions to FDA, including the use of summary reporting, for Class I devices and for Class II devices that are not permanently implantable, life supporting, or life sustaining. Some commentators sought clarification of how the status of “life-supporting” or “life-sustaining” would apply to combination products, and whether the intended use of the combination product would determine the status of the device constituent part. One commenter sought clarification of how such a class-based approach would be applied to combination products approved under NDA or BLA, for which no express classification may have been made for the device constituent part.

(Response 15) FDA issued a notice in the Federal Register (76 FR 12743, March 8, 2011) clarifying that Class I and II device manufacturers and importers must continue to submit malfunction reports in accordance with part 803, pending future action by FDA to address the malfunction reporting requirements for class I and class II devices addressed in FDAAA. Accordingly, combination product applicants for combination products that include a device constituent part, and constituent part applicants for device constituent parts, must comply with part 803 requirements as described in this rule pending such further Agency action. At this time, therefore, malfunction reporting duties are the same for all combination products that include a device constituent part, regardless of whether the combination product or device constituent part

would be considered life-supporting or life-sustaining, and regardless of whether the device constituent part would be considered a Class I, II, or III device.

(Comment 16) One commenter sought clarification of whether the periodic reports addressed in proposed § 4.103(c) should be considered “expedited” reports for purposes of this rule.

(Response 16) FDA has retitled this provision to “Other reporting requirements for combination product applicants” for clarity because it addresses periodic safety reports for drug and biologic-led combination products and also addresses under what circumstances additional reports for device-led combination products are required upon Agency request. This rule does not modify the timing of periodic safety reports. The purpose of § 4.102(d) is to clarify which combination product applicants must submit periodic safety reports and other safety reports, and what information they must include in such reports. The intent of § 4.102(d), in conjunction with § 4.102(a), (b), and (c) is to ensure that the Agency obtains complete, timely postmarketing safety information regarding combination products while avoiding unnecessary burden to applicants.

(Comment 17) One commenter proposed the reorganization of proposed 4.103(b) to parallel the structure of § 4.103(a).

(Response 17) We have not adopted this approach because § 4.102(c) is intended to address a different issue than § 4.102(b). Section 4.102(b) (like proposed § 4.103(a)) addresses requirements that constituent part applicants and combination product applicants must satisfy for their marketed products depending upon the type of application under which it received marketing authorization, and structuring the provision based on the type of application that the applicant holds provides a clear, efficient way to identify such requirements. In contrast, the

purpose of § 4.102(c) (like proposed § 4.103(b)) is to state which additional requirements a combination product applicant must satisfy based on the types of constituent parts included in the combination product, which are most clearly and efficiently listed by constituent part type (drug, biological product, or device).

D. Section 4.103--What Information Must You Share With Other Constituent Part Applicants for the Combination Product?

(Comment 18) Some commenters requested clarification of whether proposed § 4.104(a) applied if there were a single application holder for the combination product but the combination product included an article approved under another application held by another entity for independent marketing not related to the combination product. Other commenters asked for clarification of which applicants for constituent parts of combination products could be subject to proposed § 4.104(a) and (b) if the combination product were not approved under a single application. Some commenters proposed an approach under which, if there is a single application for the combination product, the holder of that application would report to FDA in accordance with proposed § 4.103, and FDA would then decide whether any other application holders for articles included in the combination product should be notified and whether to seek additional reports from them.

(Response 18) As reflected in the preamble to the proposed rule (see 74 FR 50744 at 50749 to 50750), proposed §4.104(a) was intended to apply if the constituent parts of the combination product were being marketed by different entities, including when the constituent parts received marketing authorization under separate applications held by different applicants. As explained in the response to Comment 2, we have revised the rule to apply to combination product applicants and constituent part applicants, in part to clarify which entities are subject to

it. Accordingly, we have revised this provision to clarify that it applies solely to constituent part applicants. Section 4.103 of this final rule is not intended to establish any duties for entities who hold a marketing authorization to market a product not as part of a combination product, even if the same article is part of a combination product for which another entity received marketing authorization (e.g., the second entity might have combined the article with another product to make a co-packaged or single-entity combination product, or market the article for a new use with another product as a cross-labeled combination product).

For example, if entity A holds an approved application to market a cross-labeled combination product that includes a device and a drug, and entity B holds an approved application to market the drug for a different use (i.e., not as part of the combination product), then entity A would be the combination product applicant for that combination product, and neither entity A nor B would be a constituent part applicant for that combination product. Therefore, § 4.103 would not require either entity A or B to share information with the other.

In contrast, if entity A holds an approved PMA to market a device as one constituent part of a cross-labeled combination product (i.e., entity A is the constituent part applicant for the device constituent part of the combination product), and entity B holds an approved NDA to market a drug as the other constituent part of that combination product (i.e., entity B is the constituent part applicant for the drug constituent part of the combination product), then § 4.103 would require both entities A and B to share postmarketing safety information with each other for the specified types of events relating to that combination product.

Regarding the issue of which entities would be subject to proposed § 4.104(b), we have decided to eliminate the provision as unnecessary. Constituent part applicants that receive information from another constituent part applicant must comply with the same duties under

§ 4.102(b) with respect to this information as they must with respect to any information they receive regarding a postmarketing safety issue for their product, including the duty to submit postmarketing safety reports as required.

(Comment 19) Some commenters argued that the 5-day deadline under proposed § 4.104(a) for information sharing was too short. Some commenters recommended instead tying the timeframe to the nature of the event. Some argued that it is not warranted or useful to share information automatically within a 5-day timeframe because it leaves entities little time to evaluate the information before sharing it and could result in unnecessary redundancy of reporting.

(Response 19) We disagree with these comments. The provision calls for sharing information that the constituent part applicant receives regarding an adverse event relating to the combination product, and does not require the applicant to prepare a report in accordance with any of the regulatory reporting requirements established under parts 314, 600, 606, 803, or 806. The duty under § 4.103 does not require a constituent part applicant to analyze, investigate, or organize the information or take any other actions beyond forwarding the information as received to the other constituent part applicant(s) for the combination product and maintaining certain records. Accordingly, we believe 5 calendar days is a reasonable deadline that does not impose undue burden, while enabling timely reporting by the constituent part applicant(s) with whom the information is shared.

Such an expedited sharing of information is important to ensure timely, complete reporting with regard to adverse events that may have been brought to the attention of only one constituent part applicant for a combination product. Enabling each constituent part applicant to review in a timely manner the information related to the combination product enhances

efficiency and thoroughness of reporting because each constituent part applicant evaluates the information with respect to its own constituent part and with regard to the reporting requirements applicable to that type of constituent part.

(Comment 20) Some commenters stated that the information sharing requirements of proposed § 4.104 should be eliminated; some said these requirements are unnecessary depending on the nature of the event, and likely to produce unnecessary, duplicative reporting. Some commenters proposed that the information sharing requirements under proposed § 4.104 should apply only if the event is potentially reportable and that proposed § 4.104(a) should not apply if the applicant determines that the event does not concern the other constituent part(s) of the combination product. Other commenters proposed that if it can be determined that the event is attributable to only one constituent part, then reporting requirements should apply only to the application holder for that constituent part. Some commenters proposed that the rule be revised such that, in the event that constituent parts of a combination product are being marketed under separate applications, and it is unclear which constituent part(s) contributed to the event, the rule would require compliance only with the reporting requirements for the constituent part providing the primary mode of action for the combination product.⁸ One commenter argued that requiring separate reporting to the centers responsible for each constituent part would be overly burdensome. Some commenters sought clarification for when an applicant should report to another applicant or to FDA under proposed § 4.104(a). Some commenters requested clarification regarding when FDA would notify application holder(s) for the constituent part(s) of a combination product if FDA receives information from another application holder for that

⁸ The term “primary mode of action” is defined at § 3.2 as the mode of action that provides the most important therapeutic action of the combination product, i.e., that is expected to make the greatest contribution to the overall therapeutic effects of the combination product.

combination product. One commenter proposed eliminating the option of sharing the information with FDA arguing that including FDA in the process would slow communications and not provide any benefit. One commenter proposed that subsequent information received relating to the same event be shared only with FDA or with another applicant in the same time-frame as a report would be required to be submitted to FDA.

(Response 20) The best way for the Agency to receive complete reports for combination products is to ensure that each constituent part applicant has an opportunity to review the information received regarding the specified types of events (serious injuries, deaths, and other adverse events) for the combination product. Accordingly, we disagree with the proposals to narrow or eliminate the information sharing requirement. We do not agree this requirement will produce unnecessarily duplicative reporting. The trigger for a constituent part applicant to submit a report to the Agency is not the mere act of receiving information but a determination that the event is reportable under the PMSR requirements applicable to that applicant. The Agency may receive multiple reports regarding the same event because of § 4.103 (formerly § 4.104 in the proposed rule), but this approach ensures that the Agency has the benefit of each constituent part applicant's expertise and familiarity regarding its own constituent part in assessing the information with respect to that constituent part.

Regarding the issue of sharing information with FDA as opposed to other constituent part applicants, we have eliminated the option of sharing information with FDA as unnecessary and inefficient. We agree that timely, complete reporting by each constituent part applicant is best assured by having constituent part applicants share information they receive directly with one another.

We also agree that when any constituent part applicant shares information relating to an event with the other constituent part applicant(s), the information sharing duty ends with respect to that event. When information is shared, each constituent part applicant must investigate and report to the Agency, under the applicable PMSR requirements, regarding the event as they would for any event for which they receive information. The constituent part applicants may find it helpful to share with one another additional and followup information they receive or develop relating to the event, but this is not required by this rule.

(Comment 21) Some commenters stated that disclosure of event information to another company might involve disclosure of confidential and proprietary information. One commenter proposed that the information be shared with the other applicant if practicable and if it does not raise concerns regarding confidentiality or proprietary information.

(Response 21) Section 4.103 does not require the sharing of trade secret or confidential commercial information with other constituent part applicants. Further, we have revised this section to specify that the information required to be shared concern events that involve a death or serious injury as described in § 803.3, or an adverse experience as described in § 314.80(a) or § 600.80(a). Such information is likely to be received from health care facilities, consumers, and other sources, and therefore, unlikely to contain trade secret or confidential commercial information.

In regard to the Federal Health Insurance Portability and Accountability Act (HIPAA), we note that HIPAA only applies to covered entities (i.e., health plans, covered health care providers, and health care clearinghouses), and their business associates, and thus is unlikely to apply to constituent part applicants. Moreover, even if a constituent part applicant is a HIPAA covered entity or business associate, we note that HIPAA permits the disclosure of protected

health information (PHI), such as information that identifies a particular patient, if such disclosures are required by other law. The HIPAA Privacy Rule permits the use or disclosure of PHI “to the extent that such use or disclosure is required by law and the use or disclosure complies with and is limited to the relevant requirements of such law.” 45 CFR 164.512(a)(1). Because § 4.103 of this rule requires constituent part applicants to share with each other information received, including PHI, regarding certain events related to the combination product, a constituent part applicant, which is subject to HIPAA, would be permitted by HIPAA to make such disclosure.

(Comment 22) Some commenters sought clarification of the start time for meeting the reporting deadlines under proposed § 4.104(b). One commenter recommended that it be the day the information is received from the reporter subject to proposed § 4.104(a).

(Response 22) While the content of proposed § 4.104(b) has been removed from the rule as unnecessary, we note that the start time for determining the submission deadline for postmarketing safety reports is the same as for information received from any other source, and depends on the type of report and the regulation from which the requirement for the report arises.

(Comment 23) Some commenters asked for the Agency to provide examples of the application of proposed §4.104, including guidance on what information to include in reports under this provision. One commenter asked for guidance on the process for submitting information to the Agency under proposed §4.104.

(Response 23) Section 4.103 requires the transmittal of information received. Constituent part applicants do not need to modify, organize, or evaluate the information; they must only forward the information to the other constituent part applicant(s) for the combination product. As discussed in Comment 18, we have eliminated the alternative of sharing the

information with FDA as unnecessary and inefficient. We intend to provide additional information regarding how to comply with § 4.103 in guidance.

E. Section 4.104--How and Where Must You Submit Postmarketing Safety Reports for Your Combination Product or Constituent Part?

(Comment 24) Some commenters sought clarification of how to comply with the submission requirements for different types of reports for a combination product. One commenter proposed that the rule expressly state reports be submitted to “the approved application” if there is only one reporter for the combination product. Another proposed that reports for a combination product marketed under one application be submitted to the lead center, while those for combination products marketed under separate applications for different constituent parts in some, but not all, cases be submitted to the center responsible for the particular constituent part’s application. One commenter noted a need to clarify how to make electronic submissions for combination products.

(Response 24) As discussed in section II.E (discussion of § 4.104), we have revised the rule to clarify how and where to submit postmarketing safety reports for constituent part applicants and for combination product applicants. In keeping with comments received, § 4.104(a) requires constituent part applicants to submit their reports in the same manner as any other applicant holding the same kind of application for a product (e.g., a constituent part applicant holding a PMA for a device constituent part must submit reports in the same manner as any other applicant holding a PMA for a device).

We have drawn a distinction between types of postmarketing safety reports submitted by combination product applicants. With regard to ICSRs, we have adopted an approach consistent with comments suggesting that reports be submitted to the lead center and in accordance with the

procedures associated with the application type for the combination product. Specifically, § 4.104(b) requires such combination product applicants to submit 5-day, 15-day, and malfunction reports, if required for their product, in the manner described in the PMSR regulations associated with the application type for the combination product. For example, if the combination product received marketing authorization under an NDA, then 5-day, 15-day, and malfunction reports, and all followup reports, would be submitted how and where described in part 314 for 15-day reports and followup reports to them. This approach promotes efficiency and ensures that all such reports relating to the same event are pooled together, and that multiple ICSR reporting requirements for the same event can be satisfied through a single submission (so long as that submission meets the content and deadlines for each reporting requirement).

At the same time, it is appropriate for specific components of the Agency to have the lead for addressing certain distinct types of reports, in light of such factors as the issues raised in the reports, logistical considerations for Agency response, and efficient engagement of appropriate Agency expertise. Specifically, correction or removal reports, field alert reports, and BPDRs are currently directed to specific Agency offices to ensure efficient, effective assessment and response. Accordingly, under § 4.104(b), all combination product applicants must direct field alert reports and BPDRs to the same Agency components that currently receive them, in accordance with the underlying regulations for these reports. For example, if the combination product includes a biological product, BPDRs must be submitted to the appropriate component within CDER or CBER in accordance with parts 600 and 606, based upon which of these two Centers would ordinarily have jurisdiction over the biological product included in the combination product. Part 806 does not specify where to submit correction or removal reports. Accordingly, neither does this rule, but applicants currently should submit them to the

appropriate FDA district office, unless the information is included in an ICSR for the event, as explained in response to Comment 14. See Recalls, Corrections and Removals (Devices) (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/recalls/correctionsandremovals/default.htm>).

The Agency intends to provide guidance concerning procedural and technical details of complying with these requirements, including how to comply with the Centers' electronic reporting requirements. We seek to take best advantage of information technology and other resources to maximize the benefit of PMSR while minimizing the burden.

(Comment 25) Several commenters sought guidance regarding the content, format, and completeness of applicable forms, and appropriate terminology to use with respect to different types of events and constituent parts for combination products.

(Response 25). Applicants should provide relevant information in as complete and clear a manner as possible, consistent with the parameters of the FDA form. Also, we intend to update relevant FDA forms, if appropriate, including the instructions for how to complete them, and to develop guidance that provides recommendations for meeting PMSR requirements under this rule.

F. Section 4.105--What are the Postmarketing Safety Reporting Recordkeeping Requirements for Your Combination Product or Constituent Part?

(Comment 26) A commenter proposed that the same recordkeeping requirements apply to all types of reports for a combination product.

(Response 26) We agree with the premise that a uniform set of record retention requirements apply to all reports relating to a combination product marketed by a single applicant, i.e., a combination product applicant. Accordingly, § 4.105(b) requires that

combination product applicants maintain all PMSR records for the longest time period established in the recordkeeping requirements associated with the PMSR provisions applicable to the combination product. This approach allows combination product applicants to maintain all these PMSR records for a product under one record retention scheme, and helps ensure that potentially interrelated records all remain available for events and for the combination product. Because both parts 314 and 600 currently require record retention for 10 years, at this time, all combination product applicants must retain PMSR records for at least 10 years.

In contrast to combination product applicants, constituent part applicants market only a drug, device, or biological product rather than a complete combination product. This distinction is acknowledged and reflected in the approach taken throughout the rule in establishing PMSR requirements for constituent part applicants. The requirements for record retention by constituent part applicants align with the overall approach of the rule. Specifically, § 4.105(a)(1) requires that constituent part applicants comply with the underlying recordkeeping requirements, including timeframes, established in the PMSR requirements identified in § 4.102(b) as applicable based on their product's application type. This ensures that constituent part applicants comply with the same requirements as any other applicant marketing a drug, device, or biological product.

The essential difference between constituent part applicants and other applicants for drugs, devices, and biological products is the distinct relationship of constituent part applicants' products to one another as parts of a combination product. The information sharing requirements of § 4.103 reflect this distinct relationship and the overarching need for coordination between constituent part applicants to ensure the safety and effectiveness of the combination product. As explained in section II (discussion of § 4.103), § 4.103(b) includes an explicit recordkeeping

requirement in relation to the information constituent part applicants are required to share with one another under § 4.103(a). Section 4.103 is intended to ensure complete, timely reporting for the combination product as a whole. To support this goal, while at the same time aligning the record retention requirement for the records required under § 4.103(b) with the overall approach of this rule for constituent part applicants, § 4.105(a)(2) requires constituent part applicants to maintain the specified records of information shared for the retention period established in the PMSR recordkeeping requirements for that constituent part applicant's constituent part if there is only one period established, and the longest recordkeeping requirement established in those requirements if those requirements establish more than one record retention period. We believe that this retention period will ensure that the information remains available to the applicants and the Agency for a sufficiently long period to inform investigation of events and responses to them for the combination product, and enable the Agency to assess compliance with § 4.103, without imposing undue burden on constituent part applicants. This approach also avoids the complexities of tying the retention period for records relating to the information sharing provision to the record retention requirements applicable to the other constituent part applicant(s).

G. Alternate Approaches

(Comment 27) Several commenters proposed that the Agency adopt a wholly different PMSR approach for combination products, with some supporting the Agency's proposed approach as an interim measure until a unified framework is developed either for combination products in particular or for all FDA-regulated medical products. Some commenters proposed adopting the most stringent set of PMSR requirements applicable to the combination product. Others called for developing a harmonized approach for combination products, with one

commenter calling for a public meeting to address the issue and another for such a system to be put in place after a single reporting porthole is established for all regulated products. One commenter called for FDA to develop a PMSR system for combination products consistent with Global Harmonization Task Force guidelines, International Organization for Standardization standards, and European Commission guidelines. This comment emphasized that such other approaches rely on the “primary intended action” of the combination product to determine what PMSR requirements should apply. Some commenters recommended applying only the reporting requirements applicable to the application type. One commenter emphasized challenges of complying with multiple reporting systems.

(Response 27) The Agency has considered alternate approaches to PMSR for combination products, including in relation to the public hearing held on November 25, 2002, and the workshop held on July 8, 2003. We have considered such options and presented in the preamble (74 FR 50744 at 50745 to 50747) the Agency’s reasons for pursuing the approach described in the proposed rule. In finalizing this rule, FDA again determined that the approach described in this rule allows FDA to receive complete, timely postmarketing safety information regarding combination products, which is necessary to assure the continued safety and effectiveness of such products, using established standards and systems, while minimizing unnecessary duplication and burdens on combination product and constituent part applicants.

H. Guidance and Agency Internal Coordination and Training

(Comment 28) Various commenters requested that the Agency address implementation of this rule through guidance. Commenters noted the importance of ensuring that this rule is as clear as possible. Most commenters requested that the guidance present how the rule would apply to different types of combination products and different types of events. Several

commenters requested that this guidance include a decision tree, flow charts, tables, algorithm, or other organizational and explanatory tools to clarify how to comply with the reporting requirements applicable to a combination product. One commenter asked for guidance on whether to cross-reference reports submitted to different locations, such as field alert reports and 15-day reports. Some commenters proposed that the Agency issue guidance prior to publication of this rule. One commenter called for the guidance to address how Agency personnel will coordinate to ensure compliance and how the Agency will monitor implementation of this rule's requirements. One commenter called for the Agency to ensure that the lead center has appropriate expertise to address adverse event reports for a combination product and that training, guidance, and cross-assignment of staff might be helpful in this regard. Another commenter proposed that the Agency take appropriate measures to ensure timely, effective communication between Agency components with respect to postmarketing safety reports for combination products. Some commenters also noted the importance of appropriate training and other Agency personnel considerations.

(Response 28) We intend to publish guidance that provides recommendations on how to comply with the requirements under this rule for combination product applicants and constituent part applicants, including such matters as cross-referencing of reports. We appreciate the comments received on this issue and look forward to further feedback in response to the publication of this final rule and of the draft guidance we may issue. With regard to the requests that we issue guidance prior to issuance of this final rule, we clarified and revised the rule in certain respects, and we did not believe it would be appropriate to anticipate the content of this final rule by publishing guidance concerning its content prior to its finalization.

We agree that appropriate training of Agency staff and timely, effective coordination among Agency components to address postmarketing safety reports for combination products are important efforts that the Agency continues to address.

I. Effective Date and Compliance Dates

(Comment 29) Some commenters proposed that the Agency delay the effective date for this rule, arguing that 180 days would not provide sufficient time to take steps to come into compliance, including to develop, validate, and implement new systems, alter procedures and commercial arrangements, and train staff as needed to comply with this rule's requirements. Some proposed making the effective date 1 year after issuance. One commenter proposed 2 years.

(Response 29) We do not agree that it would be appropriate to delay the effective date of this rule. However, in light of these comments, and in consideration of the costs of this rule as discussed in section VIII, we have decided to extend the compliance date with respect to certain provisions of the rule for combination product applicants and constituent part applicants, for a period of 18 months following the effective date of this rule.

The duties for both combination product and constituent part applicants under § 4.102(a) and (b), and for constituent part applicants under §§ 4.104(a) and 4.105(a)(1) are generally the same as for any other entity holding such an application for its product, and we expect all applicants subject to this rule already to be in compliance with these provisions for their products as these provisions generally refer to existing regulations that such applicants have generally followed (see 74 FR 50744 at 50745). Accordingly, the effective date for the rule is 30 days after the date of its publication and the compliance date for these provisions is the same as the effective date for this rule. However, with respect to the requirements of § 4.102(c) and (d) for

combination product applicants, the requirements of §§ 4.103 and 4.105(a)(2) for constituent part applicants, and the requirements of §§ 4.104(b) and 4.105(b) for combination product applicants, the compliance date will be 18 months following the effective date of this rule.

J. Miscellaneous.

(Comment 30) Some comments concerned coordination of various Agency activities related to adverse events including then pending Agency rulemakings concerning electronic reporting, adverse event report database management and searchability, forms referenced in this and other rulemakings, and harmonization efforts with foreign regulatory agencies.

(Response 30) The Agency has taken into account such coordination considerations. Pending FDA rulemakings were one consideration in deciding to streamline this rule by using cross-references to requirements of the underlying regulations listed in § 4.102, without repeating the substance of those requirements. As noted in section II (see discussion of § 4.101), this approach will minimize the need to revise this regulation should the underlying regulations be amended. Similar considerations have informed our determination to reference in § 4.104 the reporting procedures required in the underlying regulations. As discussed in Response 25, we intend to update relevant FDA forms, if appropriate, including the instructions for how to complete them, and to develop guidance that provides recommendations for meeting PMSR requirements under this rule.

With respect to international harmonization, we remain committed to such efforts, including with respect to PMSR requirements for combination products. A practical challenge for combination products in particular is that international collaboration and harmonization efforts are at an early stage for these products. At the same time, there is a current need to clarify FDA's PMSR requirements for this class of products. We have taken an approach that integrates

underlying PMSR approaches for drugs, devices, and biological products, which have benefited in various respects from international harmonization efforts. We are committed to continuing to work with our foreign counterparts on PMSR and other issues for combination products.

IV. Legal Authority

The Agency derives its authority to issue the regulations in proposed part 4 subpart B from 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360l, 360hh-360ss, 360aaa-360bbb, 371(a), 372-374, 379e, 381, 383, and 394, and 42 U.S.C. 216, 262, 263a, 264, and 271. For a drug approved under an NDA or an ANDA, section 505(k) of the FD&C Act (21 U.S.C. 355) requires the applicant to submit reports concerning clinical experience and other data or information with respect to the drug to FDA and to establish and maintain related records. Section 505(k) provides the Agency with authority to specify by regulation which data or information must be submitted in such reports. FDA used this statutory authority, among others, in issuing the Agency's regulation concerning postmarketing reporting of adverse drug experiences and other postmarketing reports including field alert reports. The regulations for postmarketing reporting of adverse drug experiences and for field alert reports are set forth in § 314.80 and § 314.81, respectively.

For a device, section 519 of the FD&C Act requires manufacturers and importers to establish and maintain records, make reports, and provide information, as FDA may reasonably require to assure that such device is not adulterated or misbranded and to otherwise assure its safety and effectiveness. FDA utilized this statutory authority, in addition to other authorities, in issuing the MDR regulation and the correction and removal regulation, found in parts 803 and 806, respectively.

For a biological product, section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) requires FDA to approve a BLA on the basis of a demonstration that the product is safe, pure, and potent (section 351(a)(2)(C) of the PHS Act). Section 351(a)(2)(A) of the PHS Act requires FDA to establish by regulation requirements for the approval, suspension, and revocation of BLAs. Section 351(b) of the PHS Act also prohibits falsely labeling a biological product. FDA used section 351 of the PHS Act as statutory authority, along with other sources of statutory authority, in issuing the postmarketing reporting of adverse experiences regulation for biological products. This regulation is found in § 600.80. In proposing § 600.80, FDA indicated that information made available to the Agency through the adverse experience reports contemplated under § 600.80 could establish that a biological product is not safe or properly labeled and that the license should be revoked (55 FR 11611 at 11613, March 29, 1990). FDA used section 351 of the PHS Act as statutory authority, along with other sources of statutory authority, in issuing the BPDR regulations for biological products. These regulations are found in §§ 600.14 and 606.171. In issuing these regulations, FDA stated that these reports would enable FDA to respond when public health may be at risk, provide FDA with uniform data to track trends that may indicate broader threats to the public health, and help ensure facilities are taking appropriate actions to investigate and correct biological product deviations. (65 FR 66621 at 66623, November 7, 2000).

There is considerable overlap in the PMSR requirements for drugs, devices, and biological products. The regulatory schemes for adverse event reporting for drugs and biological products are identical in most respects. The MDR regulation has many similarities to the drug and biological product PMSR regulations. Overall, the regulatory framework governing PMSR for each type of product is intended to achieve the same general goals.

Nevertheless, these three sets of regulations differ somewhat because each is tailored to the characteristics of the types of products for which it was designed. For instance, each set of regulations contains certain specific requirements pertaining to particular products or types of postmarketing safety events that are not found in the other sets of regulations. The additional requirements for combination product applicants that FDA considers necessary are as follows: 5-day reports, 15-day reports, malfunction reports, correction or removal reports, field alert reports, and BPDRs. As set forth in this rule, it is crucial that these additional requirements be met if they apply.

The legal framework underlying this proposed rule is twofold. The first is that drugs, devices, and biological products do not lose their discrete regulatory identities when they become constituent parts of a combination product. In general, the PMSR requirements specific to each constituent part of a combination product also apply to the combination product itself. Therefore, all combination products are subject to at least two sets of PMSR requirements. For example, in the case of a device and biological product combination product, the PMSR requirements applicable to devices and to biological products would apply to the combination product. However, this rule is intended to clarify that a combination product applicant may comply only with the PMSR requirements associated with the application under which the combination product received marketing authorization and certain, specified PMSR requirements associated with the other constituent part(s). Taking the example of a device-biologic combination product, if the combination product has an approved BLA, the combination product applicant (holder of the BLA) would use parts 600 and 606 to make postmarketing safety reports for the combination product. In addition, as explained in this rule, the combination product applicant must also comply with all of the specified requirements that apply to the product.

Thus, in this case, the combination product applicant must also comply with the reporting requirements for 5-day reports, correction or removal reports, and malfunction reports if the criteria for such reports are met. Under this legal framework, if you demonstrate compliance with the applicable requirements of the set of regulations (e.g., biological product PMSR) associated with the approved application (e.g., BLA), and comply with any applicable specified additional provisions (e.g., 5-day reports, correction or removal reports, and malfunction reports), you will be considered to have satisfied all applicable PMSR requirements associated with the combination product, including its constituent parts.

The legal authority for this streamlining approach is based on the following. Although combination products retain the regulatory identities of their constituent parts, the FD&C Act also recognizes combination products as a category of products that are distinct from products that are solely drugs, devices, or biological products. For example, section 503(g)(4)(A) of the FD&C Act (21 U.S.C. 353b(g)(4)(A)) requires OCP to “designate” a product as a combination product as well as to ensure “consistent and appropriate postmarket regulation of like products subject to the same statutory requirements.” Further, section 563 of the FD&C Act (21 U.S.C. 360bbb-2) governs the “classification” of products as “drug, biological product, device, or a combination product subject to section 503(g)” (emphasis added). In this respect, the FD&C Act identifies a combination product as a distinct type of product that could be subject to specialized regulatory controls. In addition, for the efficient enforcement of the FD&C Act under section 701 (21 U.S.C. 371), FDA has the authority to develop regulations to ensure sufficient and appropriate ongoing assessment of the risks associated with combination products.

The second legal framework for this rule is founded on the postmarket safety reporting regulatory scheme associated with the application under which the combination product is

approved, plus any applicable requirements associated with the additional six specified report types listed in this rule. Although similar in effect to the previously discussed framework, this approach is based on the legal authority FDA used to issue each of its three existing regulations for postmarketing safety reporting for drugs, devices, and biological products. In the context of this rule, such authority would include, but not be limited to, sections 505(k) and 519 of the FD&C Act, and section 351 of the PHS Act. Under this authority FDA is now issuing additional requirements based on the six additional specified report types. This means that in the case, for example, of a device-biologic combination product, approved under a BLA, section 351 of the PHS Act (in addition to other applicable authorities) would provide the authority for FDA to require postmarketing safety reporting in accordance with parts 600 and 606. Furthermore, section 351 of the PHS Act also would provide the authority for the Agency to require additional reporting for the device-biologic combination product (5-day reports, malfunction reports, and correction or removal reports) if the criteria for such reports are met.

V. Analysis of Environmental Impact

FDA has determined under 21 CFR 25.30(a), 25.30(h), and 25.31(a) through (c) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description and respondent description of the information

collection provisions are shown in the following paragraphs with an estimate of the annual reporting and recordkeeping burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Postmarketing Safety Reporting for Combination Products.

Description: This final rule describes the PMSR requirements for combination products. In the development of this final rule, the Agency considered the fact that a combination product is subject to the PMSR provisions applicable to its constituent parts (drug, device, and/or biological product). The Agency reviewed each set of regulations governing PMSR for new drugs (part 314), biological products (parts 600 and 606), and devices (parts 803 and 806). The review determined that each set of regulations contains many substantially similar requirements.

Given the broad similarities in the PMSR regulations, the Agency determined that, to ensure consistent, appropriate PMSR for combination products that received marketing authorization under a single application, we need only require that combination product applicants comply with the regulatory requirements for PMSR associated with the application, and with additional, specified provisions from the other set(s) of PMSR requirements applicable to the other constituent part(s) of the combination product. This approach recognizes and addresses PMSR considerations relevant to each type of constituent part of a combination product while avoiding unnecessary redundancy and burden.

Specifically, the additional reporting requirements specified in this rule, along with any associated followup reports, are: (1) Submission of a “5-day report” as described in § 803.53 if the combination product contains a device constituent part; (2) submission of a “malfunction report” as described in § 803.50 if the combination product contains a device constituent part;

(3) submission of a “correction or removal report” as described in § 806.10 if the combination product contains a device constituent part; (4) submission of a “field alert report” as described in § 314.81 if the combination product contains a drug constituent part; (5) submission of a 15-day report as described in § 314.80 or § 600.80 if the combination product contains a drug or biological product constituent part, respectively; and (6) submission of a “BPDR” as described in §§ 600.14 and 606.171 if the combination product contains a biological product constituent part.

For combination products for which the constituent parts received marketing authorization under separate applications held by different entities, the Agency has determined that compliance with the PMSR requirements associated with the application type for the constituent part is sufficient. In addition, constituent part applicants must share safety information they receive related to certain events with the other constituent part applicant(s).

We note that the PMSR information collections for drugs, biological products, and devices found in §§ 314.80, 314.81, 600.80, 600.81, 606.170, 606.171, 803.50, 803.53, 803.56, 806.10, and 806.20 have already been approved and are in effect. The pertinent PMSR information collection provisions for § 314.80(c) and (e), as well as for § 314.81(b) are approved under OMB control numbers 0910-0001, 0910-0230, and 0910-0291. The information collection provisions for §§ 600.80 and 600.81 are approved under OMB control number 0910-0308. Those for § 606.170 are approved under OMB control number 0910-0116. Those for § 606.171 are approved under OMB control number 0910-0458. The information collection provisions for §§ 803.50, 803.53, and 803.56 are approved under OMB control numbers 0910-0291 and 0910-0437. The information collection provisions for §§ 806.10 and 806.20 are approved under OMB control number 0910-0359.

While this rule serves to permit combination product applicants to comply with a streamlined subset of the PMSR requirements applicable to all of their constituent parts, we recognize that some combination product applicants have been complying with only the reporting requirements associated with their application type. As a result, the information collection described here refers to the reporting and recordkeeping requirements for the six additional report types specified in this rule. It also refers to the new information sharing and related recordkeeping requirement applicable to constituent parts marketed under separate applications.

These requirements are necessary to ensure: (1) Consistent PMSR for combination products and constituent parts, (2) that the Agency receives necessary information to promote and protect the public health, (3) appropriate ongoing assessment of risks, and (4) consistent and appropriate postmarketing regulation of combination products. This rule enables applicants to comply with these requirements while avoiding unnecessary duplicative reporting, for example, by limiting the number of PMSR requirements with which combination product applicants must comply and by authorizing applicants to submit only a single, complete report for an event even if multiple reporting duties apply to the same event.

Description of Respondents: This rule applies to combination product applicants and constituent part applicants. Any person holding the application(s) under which a combination product received marketing authorization is a combination product applicant. Any person holding an application under which a constituent part (drug, device, or biological product) of a combination product received marketing authorization is a constituent part applicant if the other constituent part received marketing authorization under an application held by a different person.

FDA estimates the burden for this information collection as follows:

Table 3--Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
4.102(c)(1)(i) Submitting 5-day reports	15	98	1470	1.21	1779
4.102(c)(1)(ii) Submitting malfunction reports	15	98	1470	1.21	1779
4.102(c)(1)(iii) Submitting correction or removal reports	20	1	20	10	200
4.102(c)(2)(i) Submitting field alerts	92	10.8	994	8	7949
4.102(c)(2)(ii) and (3)(ii) Submitting 15-day reports	1	1	1	1	1
4.102(c)(3) Submitting BPDRs	24	6	144	2	288
4.102(d)	1	1	1	1	1
Totals*					11709

Table 4.--Estimated Annual Recordkeeping Burden

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
4.103(b)/4.105(a)(2) Records of information shared by constituent part applicants	33	18	594	.1 (6 minutes)	59
4.105(b) additional record-keeping by device-led combination products	279	.45	126	.5 (30 minutes)	63
4.105(b) additional recordkeeping by drug and biologic-led combination products	186	6	1116	.5 (30 minutes)	558
Totals					680

Table 5.--Estimated Annual Third Party Disclosure Burden

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
4.103 Sharing information with other constituent part applicants	33	18	594	.35 (21 minutes)	208

Based on FDA's experience regarding receipt of postmarketing safety reports for combination products, the Agency estimates that there will be 401 reporters (who will keep corresponding records) submitting a total of 11709 reports annually under § 4.102(c) and (d) and

33 reporters (who will keep corresponding records) sharing information eighteen times annually under § 4.103. Further, FDA estimates, based on its experience with information collection regarding postmarketing safety reporting provisions for drugs, biological products, and devices, that each report (or information sharing event under § 4.103) may take from approximately 20 minutes to 10 hours, depending on report type, to prepare and submit, and from approximately 6 to 30 minutes to fulfill the corresponding recordkeeping requirements. FDA believes that there are no significant new operating and maintenance costs associated with this collection of information because, in order to legally market their products, all applicants are required to develop and maintain systems for reporting and maintaining records of postmarketing safety events. Therefore, appropriate mechanisms for PMSR should already be in place, and combination product applicants and constituent part applicants will accrue no significant additional costs to fulfill the requirements set forth here.

In addition, we estimate that there will be no significant new costs for 15-day reporting (§ 4.102(c)(2)(ii) and (3)(ii)) and periodic reporting (§ 4.102(d)(1)) under the rule because there is significant overlap between the types of events that trigger a 15-day report for drugs and biological products and the events that trigger expedited reporting for devices. We also estimate there will be no significant new costs for other non-expedited reporting (§ 4.102(d)(2)) because of the expected rarity of the agency seeking such additional information.

Before the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the Agency displays a currently valid OMB control number.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the final rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.⁹

VIII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

⁹ The rule clarifies which PMSR requirements apply when drugs, devices, and biological products are used to create combination products. The Agency notes that there are no express preemption provisions of the FD&C act applicable to prescription drugs or biological products. Section 521 of the FD&C Act (21 U.S.C. 360k) contains an express preemption provision that applies to devices; nonetheless, the Supreme Court concluded in Medtronic, Inc. v. Lohr, 581 U.S. 470, 500-01 (1996), that requirements not applicable to a particular device do not preempt State law under section 521. Device adverse event reporting requirements, like the good manufacturing practice requirements at issue in the Medtronic case, are general requirements that do not preempt under section 521 of the FD&C Act.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule essentially describes the application of existing postmarketing safety reporting regulations to certain combination products, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

The full analysis of economic impacts is available in the docket for this final rule at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

B. Summary of Costs and Benefits

The final rule will generate one-time administrative costs from reading and understanding the rule, assessing current compliance, modifying existing standards of practice, changing storage and reporting software, and training personnel on the requirements under this rule. Firms that do not currently comply with the reporting requirements specified by the final rule will also incur annual reporting costs from the submission of field alert reports, 5-day reports, malfunction reports, correction or removal reports, and biological product deviation reports, as applicable.

The annualized total costs of the rule are between \$1.36 and \$2.68 million at a 7 percent discount rate and between \$1.35 and \$2.65 million at a 3 percent discount rate.

The final rule will benefit firms through reduced uncertainty about the reporting requirements for their specific combination product and through decreased potentially duplicative reporting. The final rule will also benefit public health by helping to ensure that important safety information is submitted and directed to the appropriate components within the Agency, so that we may receive and review this important information in a timely manner for the protection of public health.

Table 6.--Summary of Benefits, Costs, and Distributional Effects of Final Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized \$millions/year				2016	7%	10 years	
					2016	3%	10 years	
	Annualized Quantified				2016	7%	10 years	
					2016	3%	10 years	
	Qualitative	Firms will benefit from reduced uncertainty about reporting requirements. The rule will benefit public health by helping to ensure Agency components' timely receipt of postmarketing safety reports.						
Costs	Annualized Monetized \$millions/year		\$1.36	\$2.68	2016	7%	10 years	
			\$1.35	\$2.65	2016	3%	10 years	
	Annualized Quantified				2016	7%	10 years	
					2016	3%	10 years	
	Qualitative							
Transfers	Federal Annualized Monetized \$millions/year				2016	7%	10 years	
					2016	3%	10 years	
	Other Annualized Monetized \$millions/year	From:			To:			
					2016	7%	10 years	
					2016	3%	10 years	
Effects	State, Local or Tribal Government:							
	Small Business:							
	Wages:							
	Growth:							

IX. References

The following references are on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. FDA Regulation of Combination Products, November 25, 2002, accessed at: <http://www.fda.gov/downloads/CombinationProducts/MeetingsConferencesWorkshops/UCM117123.pdf>.

2. Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges, July 8, 2003, accessed at: <http://www.fda.gov/ohrms/dockets/dockets/03n0203/03n0203.htm>.

3. Individual Case Study Reports, accessed at: (<http://www.fda.gov/ForIndustry/DataStandards/IndividualCaseSafetyReports/default.htm>).

List of Subjects in 21 CFR Part 4

Biological products, Combination products, Drugs, Medical devices, Regulation of combination products, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 4 is amended as follows:

PART 4--REGULATION OF COMBINATION PRODUCTS

1. The authority citation for part 4 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360l, 360hh-360ss, 360aaa-360bbb, 371(a), 372-374, 379e, 381, 383, 394; 42 U.S.C. 216, 262, 263a, 264, 271.

2. Add subpart B, consisting of §§ 4.100 through 4.105, to read as follows:

Subpart B--Postmarketing Safety Reporting for Combination Products

Sec.

4.100 What is the scope of this subpart?

4.101 How does FDA define key terms and phrases in this subpart?

4.102 What reports must you submit to FDA for your combination product or constituent part?

4.103 What information must you share with other constituent part applicants for the combination product?

4.104 How and where must you submit postmarketing safety reports for your combination product or constituent part?

4.105 What are the postmarketing safety reporting recordkeeping requirements for your combination product or constituent part?

Subpart B--Postmarketing Safety Reporting for Combination Products

§ 4.100 What is the scope of this subpart?

(a) This subpart identifies postmarketing safety reporting requirements for combination product applicants and constituent part applicants.

(b) This subpart does not apply to investigational combination products, combination products that have not received marketing authorization, or to persons other than combination product applicants and constituent part applicants.

(c) This subpart supplements and does not supersede other provisions of this chapter, including the provisions in parts 314, 600, 606, 803, and 806 of this chapter, unless a regulation explicitly provides otherwise.

§ 4.101 How does the FDA define key terms and phrases in this subpart?

Abbreviated new drug application (ANDA) has the same meaning given the term “abbreviated application” in § 314.3(b) of this chapter.

Agency or we means Food and Drug Administration.

Applicant means, for the purposes of this subpart, 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). For the purposes of this subpart, applicant is used interchangeably with the term “you.”

Application means, for purposes of this subpart, a BLA, an NDA, an ANDA, or a device application, including all amendments and supplements to them.

Biological product has the meaning given the term in section 351 of the Public Health Service Act (42 U.S.C. 262).

Biological product deviation report (BPDR) is a report as described in §§ 600.14 and 606.171 of this chapter.

Biologics license application (BLA) has the meaning given the term in section 351 of the Public Health Service Act (42 U.S.C. 262) and § 601.2 of this chapter.

Combination product has the meaning given the term in § 3.2(e) of this chapter.

Combination product applicant means an applicant that holds the application(s) for a combination product.

Constituent part has the meaning given the term in § 4.2.

Constituent part applicant means the applicant for a constituent part of a combination product the constituent parts of which are marketed under applications held by different applicants.

Correction or removal report is a report as described in § 806.10 of this chapter.

De novo classification request is a submission requesting de novo classification under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act.

Device has the meaning given the term in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Device application means a PMA, PDP, premarket notification submission, de novo classification request, or HDE.

Drug has the meaning given the term in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act.

Field alert report is a report as described in § 314.81 of this chapter.

Fifteen-day report is a report required to be submitted within 15 days as described in § 314.80 of this chapter or § 600.80 of this chapter, as well as followup reports to such a report.

Five-day report is a report as described in §§ 803.3 and 803.53 of this chapter, as well as supplemental or followup reports to such a report as described in § 803.56 of this chapter.

Humanitarian device exemption (HDE) has the meaning given the term in § 814.3 of this chapter.

Malfunction report is a report as described in § 803.50 of this chapter as well as supplemental or followup reports to such a report as described in § 803.56 of this chapter.

New drug application (NDA) has the meaning given the term “application” in § 314.3(b) of this chapter.

Premarket approval application (PMA) has the meaning given the term in § 814.3 of this chapter.

Premarket notification submission is a submission as described in § 807.87 of this chapter.

Product Development Protocol (PDP) is a submission as set forth in section 515(f) of the Federal Food, Drug, and Cosmetic Act.

§ 4.102 What reports must you submit to FDA for your combination product or constituent part?

(a) In general. If you are a constituent part applicant, the reporting requirements applicable to you that are identified in this section apply to your constituent part, and if you are a combination product applicant, the reporting requirements applicable to you that are identified in this section apply to your combination product as a whole.

(b) Reporting requirements applicable to both combination product applicants and constituent part applicants. If you are a combination product applicant or constituent part applicant, you must comply with the reporting requirements identified in paragraphs (b)(1), (b)(2), or (b)(3) of this section for your product based on its application type. If you are a combination product applicant, you are required to submit a report as specified in this paragraph unless you have already submitted a report in accordance with paragraph (c) of this section for the same event that: Includes the information required under the applicable regulations identified in this paragraph, is required to be submitted in the same manner under § 4.104, and meets the deadlines under the applicable regulations identified in this paragraph.

(1) If your combination product or device constituent part received marketing authorization under a device application, you must comply with the requirements for

postmarketing safety reporting described in parts 803 and 806 of this chapter with respect to your product.

(2) If your combination product or drug constituent part received marketing authorization under an NDA or ANDA, you must comply with the requirements for postmarketing safety reporting described in part 314 of this chapter with respect to your product.

(3) If your combination product or biological product constituent part received marketing authorization under a BLA, you must comply with the requirements for postmarketing safety reporting described in parts 600 and 606 of this chapter with respect to your product.

(c) Reporting requirements applicable only to combination product applicants. If you are a combination product applicant, in addition to compliance with paragraph (a) of this section, you must also comply with the reporting requirements identified under this paragraph as applicable to your product based on its constituent parts. If you are a combination product applicant, you are required to submit a report as specified in this paragraph unless you have already submitted a report in accordance with paragraph (b) of this section for the same event that: Includes the information required under the applicable regulations for the report identified in this paragraph; is required to be submitted in the same manner under § 4.104 of this chapter; and, unless otherwise specified in this paragraph, meets the deadlines under the applicable regulations for the report identified in this paragraph.

(1) If your combination product contains a device constituent part, you must submit:

(i) Five-day reports;

(ii) Malfunction reports; and

(iii) Correction or removal reports, and maintain records as described in § 806.20 of this chapter for corrections and removals not required to be reported.

(2) If your combination product contains a drug constituent part, you must submit:

(i) Field alert reports; and

(ii) Fifteen-day reports as described in § 314.80 of this chapter, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.

(3) If your combination product contains a biological product constituent part, you must submit:

(i) Biological product deviation reports; and

(ii) Fifteen-day reports as described in § 600.80 of this chapter, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.

(d) Other reporting requirements for combination product applicants. (1) If you are the combination product applicant for a combination product that contains a device constituent part and that received marketing authorization under an NDA, ANDA, or BLA, in addition to the information otherwise required in the periodic safety reports you submit under § 314.80 or § 600.80 of this chapter, your periodic safety reports must also include a summary and analysis of the reports identified in paragraphs (c)(1)(i) and (ii) of this section that were submitted during the report interval.

(2) If you are the combination product applicant for a combination product that received marketing authorization under a device application, in addition to the reports required under paragraphs (b) and (c) of this section, you must submit reports regarding postmarketing safety events if notified by the Agency in writing that the Agency requires additional information. We will specify what safety information is needed and will require such information if we determine

that protection of the public health requires additional or clarifying safety information for the combination product. In any request under this section, we will state the reason or purpose for the safety information request, specify the due date for submitting the information, and clearly identify the reported event(s) related to our request.

§ 4.103 What information must you share with other constituent part applicants for the combination product?

(a) When you receive information regarding an event that involves a death or serious injury as described in § 803.3 of this chapter, or an adverse experience as described in § 314.80(a) of this chapter or § 600.80(a) of this chapter, associated with the use of the combination product, you must provide the information to the other constituent part applicant(s) for the combination product no later than 5 calendar days of your receipt of the information.

(b) With regard to information you must provide to the other constituent part applicant(s) for the combination product, you must maintain records that include:

- (1) A copy of the information you provided,
- (2) The date the information was received by you,
- (3) The date the information was provided to the other constituent part applicant(s), and
- (4) The name and address of the other constituent part applicant(s) to whom you provided the information.

§ 4.104 How and where must you submit postmarketing safety reports for your combination product or constituent part?

(a) If you are a constituent part applicant, you must submit postmarketing safety reports in accordance with the regulations identified in § 4.102(b) that are applicable to your product based on its application type.

(b) If you are a combination product applicant, you must submit postmarketing safety reports required under § 4.102 in the manner specified in the regulation applicable to the type of report, with the following exceptions:

(1) You must submit the postmarketing safety reports identified in § 4.102(c)(1)(i) and (ii) in accordance with § 314.80(g) of this chapter if your combination product received marketing authorization under an NDA or ANDA or in accordance with § 600.80(h) of this chapter if your combination product received marketing authorization under a BLA.

(2) You must submit the postmarketing safety reports identified in § 4.102(c)(2)(ii) and (c)(3)(ii) in accordance with § 803.12(a) of this chapter if your combination product received marketing authorization under a device application.

§ 4.105 What are the postmarketing safety reporting recordkeeping requirements for your combination product or constituent part?

(a) If you are a constituent part applicant:

(1) You must maintain records in accordance with the recordkeeping requirements in the applicable regulation(s) described in § 4.102(b).

(2) You must maintain records required under § 4.103(b) for the longest time period required for records under the postmarketing safety reporting regulations applicable to your product under § 4.102(b).

(b) If you are a combination product applicant, you must maintain records in accordance with the longest time period required for records under the regulations applicable to your product under § 4.102.

Dated: December 14, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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