proposed rule. Under the current regulations, existing leaseholders are excepted from the introduced species prohibition if they have active lease agreements at the time of implementation of the regulation (the regulation took effect on March 9, 2009). Under the proposed rule for the GFNMS, this exemption will no longer contain a geographic restriction of Tomales Bay, and will no longer restrict new permits from being issued through the State (as opposed to through the ONMS). This prohibition would not put any current operations out of business, because they will not need to change anything about their current procedures to continue in their operations. A beneficial effect from this proposed action may result for existing and future lease holders, such as reduced administrative burden for issuance or renewal of a lease permit. Comments received on the economic impacts of this proposed rule will be summarized and responded to in the final rule.

F. Paperwork Reduction Act

This proposed rule does not contain information collections that are subject to the requirements of the Paperwork Reduction Act. Notwithstanding any other provision of the law, no person is required to respond to, nor shall any person be subject to a penalty for failure to comply with, a collection of information subject to the requirements of the PRA, unless that collection of information displays a currently valid OMB Control Number.

V. Request for Comments

NOAA requests comments on this proposed rule for 45 days after publication of this notice.

List of Subjects in 15 CFR Part 922

Administrative practice and procedure, Environmental protection, Fish, Harbors, Marine pollution, Marine resources, Natural resources, Penalties, Recreation and recreation areas, Research, Water pollution control, Water resources, Wildlife.

Dated: September 24, 2009.

William Corso,

Deputy Assistant Administrator for Ocean Services and Coastal Zone Management.

Accordingly, for the reasons set forth above, 15 CFR part 922 is amended as follows:

PART 922—NATIONAL MARINE SANCTUARY PROGRAM REGULATIONS

1. The authority citation for Part 922 continues to read as follows:

Authority: 16 U.S.C. 1431 *et seq.*

Subpart H—Gulf of the Farallones National Marine Sanctuary

2. Section 922.82(a)(10) is amended to read as follows:

§ 922.82 Prohibited or otherwise regulated activities.

(a) * * *

(10) Introducing or otherwise releasing from within or into the Sanctuary an introduced species, except:

(i) Striped bass (*Morone saxatilis*) released during catch and release fishing activity; or

(ii) Species cultivated by a mariculture activity within the area of the sanctuary lying within the seaward boundary of the State of California and authorized by a valid lease, permit, license or other authorization issued by the State.

* * * * *

Subpart M—Monterey Bay National Marine Sanctuary

3. Section 922.132(a)(12) is amended to read as follows:

§ 922.132 Prohibited or otherwise regulated activities.

(a) * * *

(12) Introducing or otherwise releasing from within or into the area of the Sanctuary lying beyond the seaward boundary of the State of California an introduced species, except striped bass (*Morone saxatilis*) released during catch and release fishing activity.

* * * * *

[FR Doc. E9–23576 Filed 9–30–09; 8:45 am]

BILLING CODE 3510–NK–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 4

[Docket No. FDA–2008–N–0424]

RIN 0910–AF82

Postmarketing Safety Reporting for Combination Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) proposes to amend the combination product regulations to set forth postmarketing safety reporting requirements for combination products. Specifically, the rule will clarify the postmarketing safety reporting requirements that apply when regulated articles (drugs, devices, and biological products) are combined to create a combination product. The proposed rule is intended to promote and protect the public health by clarifying requirements for postmarketing safety reporting for combination products, and is part of FDA's ongoing effort to ensure the consistency and appropriateness of the regulatory requirements for combination products.

DATES: Submit written or electronic comments on the proposed rule by December 30, 2009. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by November 2, 2009, (see the ''Paperwork Reduction Act of 1995'' section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA–2008–N–0424 and/or RIN number 0910–AF82, by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the ''Paperwork Reduction Act of 1995'' section of this document).

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and docket number and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For

additional information on submitting comments, see the ''Request for Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Leigh Hayes, Office of Combination Products (HFG–3), Food and Drug Administration, 15800 Crabbs Branch Way, suite 200, Rockville, MD 20855, 301–427–1934.

SUPPLEMENTARY INFORMATION:

I. Introduction
II. Description of the Proposed Rule
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E. Role of Lead Center
F. Recordkeeping Requirements
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H. Applicability of Proposed Rule to User Facilities and Importers and Distributors as Defined in 21 CFR Part 803
I. Stakeholders' Comments on Postmarketing Safety Reporting Applicable to Combination Products
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I. Introduction

As set forth in part 3 (21 CFR part 3), a combination product is a product comprised of a combination of a drug and a device; a device and a biological; a biological and a drug; or a drug, a device, and a biological. 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; (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; (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; 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.[1] This rule does not address postmarketing reporting associated with approved products that are used in combination with investigational products.

In the past decade, significant advances have been made in the development of combination products. In recognition of these advances, the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) modified section 503(g) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353(g)) to require the establishment of an Office (Office of Combination Products (OCP)) within FDA's Office of the Commissioner. The responsibilities of OCP include ensuring the prompt assignment of combination products to agency components, the timely and effective premarket review of such products, and the consistent and appropriate postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law (21 U.S.C. 353(g)(4)).

To date, the agency has not issued regulations on postmarketing safety reporting specifically for combination products. Instead, the agency has applied provisions from the applicable postmarketing safety reporting regulations for drugs, devices, and biological products. These requirements for drugs, devices, and biological products share many similarities and have a common underlying purpose, namely to protect the public health by ensuring a product's continued safety and effectiveness. However, each set of regulations has certain reporting standards and timeframes with unique requirements based upon the characteristics of the products for which the regulations were designed (i.e., for drugs, devices and biological products).

External stakeholders have expressed concern about the lack of concrete information regarding the postmarketing safety reporting regulatory requirements for combination products (see section II.I of this document for further discussion). Generally, reporters have followed the safety reporting regulations associated with the type of marketing application used to approve or clear their combination product. For example, if a new drug application (NDA) was used to approve a drug/device combination product, reporters generally submit postmarketing safety reports in accordance with part 314 (21 CFR part 314). However, if the device component of the combination product malfunctions, the reporter currently has no clear regulatory procedure to follow under part 314 when reporting this problem. This lack of regulatory clarity could lead to reporting that does not sufficiently reflect the combination nature of the product or the fact that an adverse experience may be related to a particular constituent part of a combination product. This lack of regulatory clarity could also lead to incomplete or inconsistent reporting and to FDA not receiving important safety information. This could compromise the agency's ability to make sound regulatory decisions about product safety and could jeopardize the public health.

To address these concerns, to ensure appropriate ongoing postmarketing surveillance of risks, to ensure the consistency of the agency's postmarketing regulation of combination products, to streamline requirements for reporters by avoiding duplicative reporting requirements, FDA proposes to create 21 CFR part 4, subpart B to clarify postmarketing safety reporting requirements for combination products.[2]

[1] Combinations of two investigational products as defined at § 3.2(e)(4) are outside the scope of this proposed rule. Those types of combination products are investigational only and have not yet been approved for marketing. This proposed rule applies to all combination products for which postmarketing safety reports are required.

[2] As described in the Department of Health and Human Services (HHS) Unified Agenda (72 FR 22490, April 30, 2007), FDA also plans to propose regulations on current good manufacturing practice for combination products. FDA proposes to codify those requirements in part 4, subpart A, and to codify the postmarketing safety reporting requirements for combination products in part 4, subpart B.

II. Description of the Proposed Rule

A. Background

In the development of this proposed rule, FDA considered the fact that each constituent part of a combination product is governed by one of three differing sets of reporting provisions. The agency reviewed each set of regulations governing postmarketing safety reporting for drugs (parts 310 (21 CFR part 310) and 314), biological products (parts 600 and 606 (21 CFR parts 600 and 606)), and devices (part 803 (21 CFR part 803)). This review determined that each set of regulations contains many substantially similar requirements as well as certain important differences.

In general, each set of regulations requires reports of death and serious adverse events; each provides for periodic and followup reports; and each provides a method to signal certain types of safety events that warrant expedited reporting. Because of these similarities, it is possible to consolidate the requirements so that the combination product is subject primarily to the reporting requirements associated with the type of marketing application under which the product is approved or cleared. However, there are certain significant differences in the three sets of regulations. These differences are designed to facilitate adverse experience reporting that adequately addresses the distinct characteristics and potential safety issues related to a particular type of product (i.e., drug, device, and biological product). 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 type of marketing application. FDA has identified five such provisions, unique to drugs, biologics, or devices, that need to be preserved to appropriately reflect the combination nature of the product and to ensure consistent and appropriate postmarketing safety reporting for combination products:

1. 5-Day Report

The Medical Device Reporting (MDR) regulation has a provision found in § 803.53(a), which requires reporting no later than five work days after the day the reporter becomes aware that an MDR reportable event associated with the device necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. This section also allows FDA to make written requests for the submission of all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request. Reporters must also maintain a record of any report they submit under this provision. This provision is unique to devices; a similar provision is not found in the drug or biological product reporting regulations.

2. 30-Day Device Malfunction Report

The MDR regulation also includes § 803.20(b)(3)(ii), which requires reporting no later than 30 calendar days after the day the reporter becomes aware of information that reasonably suggests the device has malfunctioned and that this device or a similar device that the reporter markets would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.[3] Reporters must also maintain a record of any report they submit under this provision. Like the 5-day MDR report, this situation is unique to devices, and the drug and biological product reporting regulations do not have comparable provisions.

3. 15-Day ''Alert Report'' for Drugs and Biological Products

A reporter must submit to FDA a report of an adverse experience associated with the use of a drug or biological product that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 days of initial receipt of the information as set forth in §§ 314.80(c)(1) and (e), and 600.80(c)(1) and (e). Serious events are reportable within 30 days under § 803.20(b)(3)(i) for devices, regardless of whether or not they are expected. However, there is no requirement in the MDR regulation for expedited (15-day) reporting of an event that is both serious and unexpected.

4. 3-Day Field Alert Report

Another unique provision is § 314.81(b)(1), which requires applicants to file ''field alert reports'' when there is information concerning certain types of problems with a drug in distribution, such as any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in a distributed drug product, or any failure of one or more distributed batches of the drug to meet the specification established for it in its marketing application, or any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article. Reporters must submit this information to the FDA district office that is responsible for the facility involved within 3 working days of its receipt. They must provide the information by telephone or other rapid communication means, with prompt written followup. Reporters must also maintain a record of any report they submit under this provision. These types of situations are specific to drug products, and neither set of regulations found in parts 600 (biological products) or 803 (devices) has a similar provision requiring expedited submission of these types of reports.

5. Expedited Blood Fatality Report

Section 606.170 requires expedited reporting of a complication of blood collection or transfusion confirmed to be fatal, by telephone, facsimile, express mail or electronically transmitted mail as soon as possible, and a written report within 7 days after the fatality. Reporters must also maintain a record of any report they submit under this provision. This situation is specific to blood products. Although parts 310, 314, 600 and 803 require expedited reporting of deaths, they do not provide for the immediate notification of blood-related fatalities.

B. General Principles

Given the broad similarities in the regulations, the agency believes that the simplest and most straightforward way to ensure that combination products are regulated consistently is by continuing to require reporters to comply with the requirements for postmarketing safety reporting associated with the application used to approve or clear their combination product (proposed § 4.103(a)), as long as the five unique specified provisions particular to each different set of regulations are, in fact, complied with by the reporter (proposed § 4.103(b)). This supplementation reflects the combination nature of the product, and recognizes and preserves each constituent part's unique characteristics. Specifically, these unique reporting requirements, along with any associated followup reports, are as follows: (1) submission of a ''5-day report'' related to the device constituent part of a combination product as described in § 803.53(a); (2) submission of a 30-day ''malfunction report'' related to the device constituent part of a combination product as described in section 227 of FDAAA and § 803.20(b)(3)(ii); (3) submission of a

[3] Section 227 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended section 519(a)(1) of the FD&C Act (21 U.S.C. 360i) to require 30-day malfunction reports under part 803 for only certain devices, such as class III devices and class II devices that are permanently implantable, life supporting, or life sustaining. Other devices, such as class I devices, are subject to summary reporting on a quarterly basis. See the proposed definition of malfunction report in proposed §§ 4.101 and 4.103(b)(2).

''postmarketing 15-day 'Alert report'''' associated with the use of a drug or biological product constituent part of a combination product, as described in §§ 314.80(c)(1) and (e), and 600.80(c)(1) and (e); (4) submission of a 3-day ''field alert report'' as described in § 314.81(b)(1); and (5) submission of an expedited ''blood fatality report'' as described in § 606.170.

Given the unique nature of combination products, more than one applicant may be involved in the development of a combination product, or more than one marketing application may be submitted. For most combination products, however, a single marketing application is submitted for the combination product's approval, clearance or licensure. In these cases, the marketing application covers all constituent parts of the combination product (e.g., both the drug and device constituent parts of a drug-device combination product). The applicable reporting requirements for this type of circumstance are described later in this section (section II.B of this document). In some cases, however, separate marketing applications are submitted for the various constituent parts of a combination product. This can occur when one applicant submits separate marketing applications for the various constituent parts of a combination product (e.g., an NDA for the drug constituent part and a premarket approval application (PMA) for the device constituent part), or when a combination product is developed by more than one applicant, each of which holds a marketing application for its respective constituent part of the combination product. For this type of circumstance, the applicable reporting requirements are described in section II.G of this document.

Under the proposed rule, combination products marketed under a single application would be subject to the following reporting scheme:

1. General Requirements (Proposed § 4.103(a))

A reporter would use the requirements for postmarketing safety reporting associated with the approved or cleared application under which the combination product is marketed. In general, for combination products approved or cleared under the device provisions of the FD&C Act, a reporter would utilize medical device reporting under part 803; for combination products approved under the drug provisions of the FD&C Act, a reporter would use §§ 314.80 and 314.81; and for combination products licensed under the Public Health Service Act (PHS Act), a reporter would use §§ 600.80 and 606.170. If you are the only reporter for a combination product (i.e., another reporter is not responsible for reporting for one of the constituent parts of the combination product), you would consider the combination product as a whole (i.e., all of its constituent parts) and the application under which it is approved or cleared when determining whether an event is required to be reported.

2. Additional Requirements (Proposed § 4.103(b))

When applicable, depending on the type of combination product and the nature of the reportable event, a reporter would submit additional types of reports and any associated followup reports, to appropriately reflect the combination nature of the product. These five types of reports, described above, would only be necessary if you would not otherwise (already) be required to provide them under the reporting framework associated with the application under which your product is approved, or if they would be required, but at a later timeframe.

3. Multiple Reporters (Proposed § 4.104)

If you are not the only reporter for a combination product (e.g., you hold an application for one constituent part of the combination product, while another reporter holds an application for its other constituent part), you are subject to applicable requirements for postmarketing safety reporting for your constituent part of the combination product. In addition, to ensure the other reporter is aware of and can investigate and followup on events you may learn about, you must submit the information you receive about events to FDA or the other reporter within 5 calendar days of your receipt of the information. In turn, you must investigate and report information you receive about reportable events provided to you by FDA or another reporter for your combination product.

4. Submission and FDA Review of Reports (Proposed § 4.105)

With the exception of ''field alert reports'' that are submitted to the appropriate FDA district office, all reports, including the reports associated with the regulatory requirements applicable to your product or constituent part, and the additional types of reports (described previously) reflecting the combination nature of the product, would be submitted using the submission methods identified in the appropriate underlying regulations. The lead FDA center charged with review and regulation of the combination product will review the reports and may consult with other Centers as needed.

5. Recordkeeping Requirements (Proposed § 4.106)

Records would be kept in accordance with the existing underlying regulatory requirements applicable to each type of report.

C. Specific Examples

1. Drug/Device (Approved Under Section 505 of the FD&C Act)

The proposed rule would preserve the unique postmarketing safety reporting requirements for drugs, devices, and biological products regardless of the type of marketing application for the combination product. For example, for a drug/device combination product regulated under the drug provisions of the FD&C Act and approved under an NDA, a reporter would follow the NDA reporting provisions set forth in §§ 314.80, 314.81, 314.98, or 314.540, as is the case for all products regulated under part 314. Although the language of part 314 refers specifically to the drug product, under the proposed rule, if you are the only reporter for the combination product, you would consider the combination product as a whole (i.e., all of its constituent parts including its device constituent parts) and the application under which it was approved or cleared when determining the reportability of an event under § 314.80(c)(1) (15-day alerts report). For example, an event that is both serious and unexpected, whether associated with the drug or device constituent part of the combination product, would be reported within 15 calendar days of initial receipt of such information by the reporter.

A reporter for a drug/device combination product, approved under an NDA, would also be required to submit a reportable device malfunction or a 5-day report when necessary for an event related to the device constituent part of their combination product, and to include such reports in the periodic reports submitted under § 314.80(c)(1). For example, a 30-day device malfunction report would be necessary when a reporter becomes aware of information that reasonably suggests that the device constituent part of the combination product malfunctioned and if the malfunction were to recur, it would be likely to cause or contribute to a death or serious injury. In that case, a reporter would submit, as appropriate, a malfunction report as described in section 227 of FDAAA, as well as any required followup reports. Similarly, a

reporter would submit a 5-day report, as defined in § 803.3 and described in § 803.53(a), if there is a reportable event regarding a device constituent part of a combination product that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. In either case, since the drug/device combination was approved under an NDA, the report would be submitted to the address specified in part 314. Any report submitted to FDA would also be described in the periodic reports required by § 314.80(c)(2).

2. Biological Product/Device (Approved Under Section 351 of the PHS Act)

The specified device reporting requirements would be similarly applied, as described in section II.C.1 of this document, if a biological product/device combination product is approved under a biologics license application (BLA). A reporter would follow the biologics reporting provisions set forth in §§ 600.80 and 606.170 (for products with blood or blood component constituent parts) as would be the case for any product licensed under section 351 of the PHS Act. In general, reporting under § 600.80 would also cover the device constituent part, not including 5-day MDR reports and 30-day MDR malfunction reports. As stated in the previous example, if you become aware of information that reasonably suggests that the device constituent part of the combination product malfunctioned and that if the malfunction were to recur it would be likely to cause or contribute to a death or serious injury, you would submit a 30-day malfunction report as described in section 227 of FDAAA, and any required followup reports. Likewise, you would submit a 5-day report for a reportable event regarding a device constituent part of a combination product that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. Since the biological product/device combination was approved under a BLA, the reports would be submitted as described in § 600.80 and to the address specified in § 600.2. A reporter would also describe any 5-day and malfunction reports submitted to FDA in the periodic reports required by § 600.80(c)(2).

3. Drug or Biological Product/Device (Approved or Cleared Under the FD&C Act's Device Authorities)

The proposed rule would also preserve the unique reporting requirements relevant to drugs and biological products that may be constituent parts of a combination product, if the combination product is regulated under the device provisions of the FD&C Act. For example, if a drug/device combination product is approved under a PMA or cleared under a premarket notification (510(k)), you would comply with the applicable postmarketing safety reporting requirements set forth in part 803, as you would for other products regulated under the device provisions of the FD&C Act. Although the language of part 803 refers specifically to devices, under the proposed rule, if you are the only reporter for the combination product, you would, in general, submit postmarket safety reports for the combination product, including its drug or biological constituent parts, under part 803. You would also comply with the 15-day alert report requirements, under §§ 314.81(c)(1) or 600.80(c)(1), for the drug or biological product constituent parts, if such requirements applied. In addition, you would comply with a 3-day field alert report, for the drug constituent part, if § 314.81(b)(1) applied. For example, if a death or serious injury occurred, whether associated with the drug or device constituent part of the combination product, you would report it in accordance with part 803. However, if a serious, unexpected adverse experience occurred that is associated with the use of the drug constituent part of the combination product, you would investigate and submit a ''postmarketing 15-day 'Alert' report,'' and any required followup reports, as described in § 314.80(c)(1).[4] A 30-day MDR report for this event would not be required. Likewise, if you receive a report that there is bacteriological contamination of the drug constituent part of your distributed combination product, or another type of event described in § 314.81(b)(1) related to the drug constituent part of your distributed combination product, you would submit a field alert report to the appropriate FDA district office within 3 working days of your receipt of the information.

Similarly, the proposed rule would also preserve the unique reporting requirements relevant to blood-related fatalities. If a device/biological product combination product containing blood or a blood component was approved under a PMA, a reporter would follow the reporting requirements described in part 803. However, a reporter would instead submit a ''postmarketing 15-day 'Alert' report'' as described in § 600.80(c)(1) for a serious, unexpected adverse experience associated with the use of the biological product constituent part of the combination product. A 30-day MDR report for this event would not be required. Similarly, a reporter would submit a report, as described in § 606.170, for a blood-related fatality. Since the device/biological product combination was approved under a PMA, the reports would be submitted to the address specified in part 803.

4. Drug/Biological Product (Approved Under Section 505 of the FD&C Act or Section 351 of the PHS Act)

Drug and biological product reporting requirements are very similar, with two exceptions being § 606.170, the provision which concerns expedited reporting of blood-related fatalities and § 314.81(b)(1) the provision which concerns reporting of certain types of problems with a drug in distribution, such as bacteriological contamination, a significant change in or deterioration of the drug, failure of the drug product to meet application specifications, or an incident that causes the drug product or its labeling to be mistaken for, or applied to, another article. A reporter with a drug/biological combination product approved under a BLA would be required to follow the postmarketing safety reporting procedures set forth in parts 600 and 606 (for a combination product with a blood or blood component constituent part). Compliance with these provisions would satisfy the reporting requirements for an adverse experience that is associated with the use of either the drug or biological product constituent parts of the combination product, unless you receive information of the type described in § 314.81(b)(1) concerning the drug constituent part of the product, in which case you would submit a ''field alert report.'' Similarly, a reporter with a drug/biological combination product approved under an NDA would follow the postmarketing safety reporting provisions described in part 314. Compliance with these provisions would satisfy the reporting requirements for an adverse experience associated with the use of either the drug or the biological product constituent part, unless the biological product constituent part contained blood or a blood component. In that case, if you have a drug/biological combination product that contained blood or a blood component approved under a NDA, you would comply with part 314, and, if applicable, submit an expedited blood fatality report as described in § 606.170. Reporting the

[4] Even though, in this example, the combination product is approved under the device authorities, you would submit a 15-day alert report, if required, for the drug constituent part, regardless of whether the drug constituent part ''caused or contributed to'' a reportable event.

event within the timeframe set forth in § 606.170 would also fulfill your requirement to report a serious, unexpected event within 15 days under § 314.80(c)(1).

D. Additional Considerations

FDA does not expect or desire that reporters submit duplicate reports, and this proposal is intended to ensure that duplicative reporting does not occur. Under this proposal, take, for example, a reporter who submits a 15-day alert report for a serious, unexpected adverse experience associated with the use of a drug constituent part of a drug/device combination product approved under a PMA and subject to part 803 as discussed previously (the reporter would follow the reporting requirements, standards and timeframes specified in part 803). In this case, submission of the 15-day alert report and any associated followup reports would fulfill the requirement for submission of a 30-day report under part 803 for a serious event, regardless of whether or not it was expected. In other words, reporting the serious, unexpected event that is associated with the drug constituent part of your combination product within 15 days would also fulfill your requirement to report a serious event, regardless of expectedness, within 30 days under the MDR regulation. Similarly, if the combination product is comprised of a biological product component containing blood and a drug component, submission of a ''blood fatality report'' and any associated followup reports, as soon as possible and with a written report within 7 days, would satisfy the requirement to report a death or serious injury within 15 days under part 314.

We note that this proposed rule applies to mandatory safety reports submitted to the agency, i.e., those reports currently submitted on Form 3500A or the CIOMS I or Vaccine Adverse Event Reporting System (VAERS) form, or their electronic equivalents, periodic safety reports, as well as ''field alert reports'' related to the drug constituent part of a combination product. This proposed rule does not change any annual or periodic reporting timeframes. Furthermore, the regulations proposed here do not supersede other reporting requirements found in 21 CFR parts 314, 600, 606, 803, or 806. Finally, FDA's authority to require additional postmarketing safety reporting for a particular product under other regulatory provisions, e.g., conditions of approval or postmarketing commitments, is unaffected by this rule.

E. Role of Lead Center

For a combination product approved or cleared under one marketing application, the ''lead'' Center, i.e., the Center with primary responsibility for the review and regulation of the combination product, will have lead responsibility for review of all postmarketing safety reports, regardless of whether a particular constituent part is associated with the event. After the lead Center receives the postmarketing safety report, it will consult as needed with the other Center(s).

For example, for a drug/device combination product approved under an NDA by the Center for Drug Evaluation and Research (CDER), all reports required by part 314 under proposed § 4.103(a), as well as under the two unique specified provisions for devices (5-day or 30-day device malfunction reports) under proposed § 4.103(b)(1) and (b)(2), would be submitted to the address required for all other postmarketing safety reports the reporter submits (in this case, those required by part 314). CDER would have the lead on their review, and CDER would consult the Center for Devices and Radiological Health (CDRH) as needed.

F. Recordkeeping Requirements

In considering the recordkeeping requirements that should apply for postmarketing safety reporting for combination products, the agency chose to use the time periods set forth in the regulations for drugs, devices, and biological products because both stakeholders and the agency are familiar with those requirements. As a result, under proposed § 4.106(a), records pertaining to reportable events under parts 310, 314 and 600 would be kept for 10 years, and records for reportable events under part 803 would be kept for 2 years or the expected life of the combination product, whichever is longer. Under proposed § 4.106(b), the recordkeeping requirements for the five additional provisions specified in proposed § 4.103(b) would each be the same as those currently required by the underlying regulations from which these requirements were derived.

G. Separate Applications and/or Reporters

For some combination products, separate marketing applications are submitted for the individual constituent parts of a combination product. In some cases, one reporter holds all the applications used to approve or clear the combination product; in other cases, the reporter holds only one application that governs one constituent part of the combination product, while a different reporter holds the application for the other constituent part.

Under proposed § 4.103(a), if you are the only reporter for a combination product, you would consider each of the reporting requirements specified in proposed § 4.103(a) and comply with each that is applicable to your combination product or constituent part. For example, if you hold a single marketing application covering the entire combination product, under proposed § 4.103(a), you would be subject primarily to the set of reporting requirements associated with that type of marketing application (e.g., part 803 if your product is approved under a PMA). However, if you hold two marketing applications for your combination product (e.g., an NDA for the drug constituent part and a PMA for the device constituent part), under proposed § 4.103(a), you would be subject to the reporting requirements under part 803 for your device constituent part, and to the reporting requirements under part 314 for your drug constituent part. In the special circumstance of holding two marketing applications for your combination product, and you can reasonably determine the constituent part that caused the adverse event, you only consider that particular constituent part when determining your reporting requirements. For example, if you hold multiple marketing applications for a combination product and you reasonably conclude that the adverse event was related to the drug constituent part, you would only follow the reporting requirements under part 314. Similarly, if the adverse event was related to the device constituent part, you would only follow the reporting requirements under part 803; if the adverse event was related to the biological product constituent part, you would only follow the reporting requirements under parts 600 and 606. If it is unclear which constituent part led to the adverse event, you would satisfy reporting requirements for each constituent part of the combination product.

If you do not hold all of the applications used to approve or clear the constituent parts of your combination product, you would comply with the requirements for postmarketing safety reporting associated with the application used to approve or clear your constituent part of the combination product. Additionally, under proposed § 4.104(a), you would submit the information you receive about an adverse event to FDA or the reporter for the other constituent part of

the combination product within 5 calendar days of your receipt of the information. Under proposed § 4.104(b), if the other reporter receives such information from you, that reporter would then investigate and report the event in accordance with the statutory provisions and regulatory requirements for postmarketing safety reporting for their constituent part of the combination product. For example, if you hold the application for a drug constituent part of a drug/device combination product approved under an NDA, and you receive information regarding an event, you would comply with part 314, i.e., the reporting provisions associated with your application, in determining reportability of the event. You would also send the information about the event to FDA or the reporter for the device constituent part of the combination product within 5 calendar days of receiving the information. If you choose to notify the device reporter within 5 calendar days, the device reporter would investigate and report the event in accordance with part 803, i.e., the reporting provisions associated with that reporter's application. In some cases, the regulations will not require the other reporter to submit the report; in other circumstances, depending on the nature of the reportable event, the regulations will require the other reporter to submit a report. FDA recognizes that in these relatively rare circumstances, the agency may receive duplicate reports regarding one incident. However, FDA believes these requirements are necessary in order to promote and protect the public health by ensuring consistent and appropriate ongoing postmarketing surveillance of risks, and ensure both manufacturers are aware of and appropriately investigate and follow up on events involving their constituent part(s) of a combination product.

H. Applicability of Proposed Rule to User Facilities and Importers and Distributors as Defined in Part 803

The proposed rule does not apply to user facilities required to report to FDA under part 803. Section 803.30 requires user facilities to report deaths to FDA and serious injuries to the device manufacturer within 10 days. Since user facility reporting already includes early, expedited reporting of deaths and serious injuries, it encompasses the types of additional reports described in proposed § 4.103(b) related to drug and biological product constituent parts, i.e., serious and unexpected adverse experiences and blood-related fatalities. Therefore, no further supplementation is necessary in order for user facility reporting to reflect the combination nature of a product.

The proposed rule also does not apply to distributors as defined in part 803, i.e., those who further the marketing but do not repackage or otherwise change the container, wrapper, or labeling. Under § 803.18(d), device distributors are required to maintain records of incidents but not to report to FDA.

Importers of combination products subject to part 803 would be subject to the proposed rule. Under part 803, importers are required to report deaths and serious injuries to FDA, and device malfunctions to the manufacturer.[5] Importers of combination products regulated under the device provisions of the FD&C Act would continue to be subject to part 803. Such importers would submit to FDA reports described in proposed § 4.103(b) to provide for earlier, expedited reporting of serious, unexpected adverse experiences associated with the drug or biological product constituent parts of a combination product they are importing. Importers would also submit expedited reporting of fatalities related to a blood constituent part of the imported combination product.

I. Stakeholders' Comments on Postmarketing Safety Reporting Applicable to Combination Products

FDA held a public hearing on November 25, 2002, and a public workshop on July 8, 2003, to discuss various issues pertaining to combination products, including postmarketing safety reporting for combination products. Stakeholders provided a number of thoughtful written comments, regarding postmarketing safety reporting, to a docket, which FDA opened to further facilitate the discussion of combination product issues. The agency has carefully reviewed all the comments we received, and we have considered them in the development of this proposed rule. Two common themes that emerged from the comments were: (1) The need for consistency in reporting requirements and (2) avoidance of duplicative reporting. We believe that the provisions set forth in this proposal provide a framework that adequately addresses these concerns.

Some stakeholders have suggested that FDA consider developing an entirely new postmarketing safety reporting scheme for combination products. Such a scheme might, for example, harmonize the varying definitions, reporting standards, timeframes, and other differences between the postmarketing safety reporting regulations for drugs, devices, and biological products. However, as described previously, given the broad similarities in the regulations, the agency determined that the simplest and most straightforward approach is to continue to require reporters to comply with the requirements for postmarketing safety reporting associated with the application used to approve or clear the combination product, as long as there is compliance, as appropriate, with the five unique provisions. This approach recognizes and preserves each constituent part's unique characteristics, while allowing reporters and FDA to continue to use mechanisms for reporting that are currently in practice.

Finally, some stakeholders have recommended that the agency develop a comprehensive information technology (IT) system for postmarketing safety reporting of combination products. The agency acknowledges the need to make IT accommodations to have its postmarketing safety reporting procedures work efficiently. The agency is developing an internal electronic infrastructure for combination product safety reports. We anticipate that we will be able to implement this infrastructure prior to the effective date of any final rule based on this proposed rule. In parallel with that project, we are currently enhancing mechanisms for FDA to receive combination product postmarketing safety reports electronically and for intercenter consultation of these reports upon their receipt. Additionally, we recognize that it may be necessary to make minor changes to the Form FDA 3500A, the VAERS form, the periodic safety report, the Form FDA 3331, and Form FDA 3486, or their electronic equivalents and/or instructions to accommodate the postmarketing safety information required by this rule. We invite comment on what changes might be necessary and will provide further instructions for practical implementation in conjunction with any final rule that may issue after this proposed rule.

FDA believes these proposed postmarketing safety reporting requirements will ensure the consistency and appropriateness of postmarketing safety reporting for combination products. The rule provides that, regardless of the type of marketing application used to approve or clear the product or the Center with primary responsibility for its review, each combination product will be

[5] Under section 227 of FDAAA, if an importer is required, under part 803, to submit a report concerning a device malfunction to the manufacturer, the importer must submit the report to the manufacturer in accordance with part 803.

subject to similar postmarketing safety reporting requirements. The rule recognizes and incorporates the similarities of the reporting requirements in the different sets of regulations, while also ensuring appropriate reporting by recognizing and preserving the unique provisions which embody necessary safety signals, given the combination nature of the product. These safety reporting requirements will help ensure the submission of necessary and appropriate information to expedite FDA's safety review and evaluation, and thereby will enhance the agency's ability to promote and protect the public health. The proposed rule when finalized will affect postmarketing safety reports submitted on or after the effective date of any final rule issued as a result of this proposed rule.

III. Legal Authority

The agency derives its authority to issue the regulations in proposed 21 CFR part 4 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, Federal Food, Drug, and Cosmetic Act, and 42 U.S.C. 216, 262, 263a, 264, and 271, Public Health Service Act. Of these, certain authorities are particularly significant. For a drug approved under an NDA or an abbreviated new drug application, section 505(k) requires the applicant to submit reports, concerning clinical experience, 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. This regulation is set forth in § 314.80.

For a device, section 519 of the FD&C Act (21 U.S.C. 360i) 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, found in part 803.

For a biological product, section 351 of the 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) also prohibits falsely labeling a biological product. FDA used section 351 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).

There is considerable overlap in the postmarket safety reporting requirements for drug, 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 postmarket safety reporting regulations. Overall, the regulatory framework governing postmarket safety reporting 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 adverse events, which are not found in the other sets of regulations. These are as follows: MDR 5-day Reports, MDR 30-day malfunction reports, Drugs/Biologics 15-day alert reports, Drugs 3-day field alert reports, and Expedited Blood Fatality Reports. As set forth in this proposal, it is crucial that these 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 discreet regulatory identities when they become constituent parts of a combination product. In general, the postmarket safety reporting 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 postmarketing safety reporting requirements. For example, in the case of a device and biological product combination product, the MDR regulation in part 803 and the biological product postmarket reporting of adverse experiences regulation in § 600.80 would apply to the combination product. However, this proposed rule is intended to clarify that a reporter must only comply with the postmarketing safety requirements associated with the application used to approve or clear the combination product. In the example above of a device-biologic combination product, if the combination product has an approved BLA, the reporter would use § 600.80 to report postmarketing adverse experiences for the combination product. In addition, as explained in this proposal, the reporter must comply with whichever of five specific requirements apply. In the case of a device-biologic combination product with an approved BLA, the reporter would also have to file MDR 5-day Reports and MDR 30-day malfunction reports if the criteria for such reports were met. Under this legal framework, if you demonstrate compliance with the applicable requirements of the set of regulations (e.g., biological product postmarket safety reporting) associated with the approved application (e.g., BLA), and comply with any applicable specified unique provisions (e.g., MDR 30-day malfunction reporting), you will be considered to have satisfied all applicable requirements from the other set of reporting regulations (e.g., MDR regulation).

The legal authority for this 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, requires the Office of Combination Products (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, 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, 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 the proposed rule is founded on the postmarket safety reporting regulatory

scheme associated with the application, under which the product is approved, plus any applicable requirements of the five unique reporting provisions listed in this proposal. Although similar in effect to the first framework described previously, this approach is based on the legal authority FDA used to issue each of its three existing regulations for postmarket safety reporting for drugs, devices, and biological products. In the context of this proposal, 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 five unique reporting provisions. 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 postmarket safety reporting under § 600.80. Furthermore, section 351 would provide the authority for the agency to require additional reporting for devices (MDR 5-Day Reports and MDR 30-Day Malfunction Reports if the criteria for such reports are met).

This legal theory applies to all combination products subject to this proposal. It is particularly relevant, however, for those combination products involving a drug constituent part and approved under a BLA or approved or cleared under the device authorities. This is because section 505(k) of the FD&C Act requires the submission of reports ''in the case of any drug for which an approval of an application filed under subsection (b) or (j) [of section 505] is in effect * * *''.

IV. Environmental Impact

FDA has determined under 21 CFR 25.30(a), 25.30(h), 25.30(j), 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.

V. Paperwork Reduction Act Analysis

This proposed rule contains information collections that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below with an estimate of the annual reporting and recordkeeping burden. 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.

FDA invites comments on the following topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Postmarketing Safety Reporting for Combination Products

Description: This proposed rule clarifies postmarketing safety reporting requirements for combination products. In the development of this proposed rule, the agency considered the fact that each constituent part of a combination product is governed by one of three differing sets of reporting provisions for drugs, devices, and biological products. The agency reviewed each set of regulations governing postmarketing safety reporting for drugs (parts 310 and 314), biological products (parts 600 and 606), and devices (part 803). The review determined that each set of regulations contains many substantially similar requirements. Given the broad similarities in the regulations, the agency determined that the simplest and most straightforward way to ensure that combination products are regulated consistently is by continuing to require reporters to comply with the regulatory requirements for postmarketing safety reporting associated with the application used to approve or clear the combination product, as long as the five unique provisions particular to each different set are also applied. This supplementation reflects the combination nature of the product, and recognizes, preserves, and distinguishes each constituent part's unique characteristics. Specifically, these unique reporting requirements, along with any associated followup reports, are: (1) submission of a ''5-day report'' related to the device constituent part of a combination product as described in § 803.53(a); (2) submission of a 30-day ''malfunction report'' related to the device constituent part of a combination product as described in section 27 of FDAAA and § 803.20(b)(3)(ii); (3) submission of a ''postmarketing 15-day 'Alert report''' for a serious, unexpected adverse experience associated with the use of a drug or biological product constituent part of a combination product, as described in §§ 310.305(c), 314.80(c)(1) and (e), and 600.80(c)(1) and (e); (4) submission of a 3-day ''field alert report'' related to the drug constituent part of a combination product as described in § 314.81(b)(1); and (5) submission of an expedited ''blood fatality report'' concerning a fatality related to the blood or blood component constituent part of a combination product as described in § 606.170.

We note that the postmarketing safety reporting information collections for drugs, biological products, and devices found in §§ 314.80, 314.81, and 600.80, 600.81, 606.170, 803.20, and 803.53 have already been approved and are in effect. The pertinent postmarketing safety reporting information collection provisions for § 314.80(c) and (e), as well as for § 314.81(b) are approved under OMB Control No. 0910–0001, which expires May 31, 2011, OMB Control No. 0910–0230, which expires July 31, 2012, and OMB Control No. 0910–0291, which expires December 31, 2011. The information collection provisions for §§ 600.80 and 600.81 are approved under OMB Control No. 0910–0308, which expires on September 30, 2011. Those for § 606.170 are approved under OMB Control No. 0910–0116, which expires February 29, 2012. Finally, the information collection provisions for §§ 803.20 and 803.53 are approved under OMB Control No. 0910–0437, which expires on July 31, 2012. As a result, the information collection described here refers only to the reporting and recordkeeping requirements for the five unique reporting requirements that are being applied because the product is a combination product. FDA does not expect or desire that reporters submit duplicate reports, and this proposal is intended to ensure that duplicative reporting does not occur.

These proposed requirements are necessary to: (1) Ensure consistent postmarketing safety reporting, (2) ensure that the agency receives necessary information to promote and protect the public health, (3) avoid duplicative reporting, (4) ensure appropriate ongoing assessment of risks, and (5) ensure consistent and appropriate postmarketing regulation of combination products.

Description of Respondents: Any person required to submit or record a reportable event under §§ 310.305, 314, 600, 606, or 803, except for user facilities and device distributors as defined in part 803.

Proposed § 4.103(b)(1) requires reporters for combination products comprised of a device constituent part to report no later than 5 work days after the day the reporter becomes aware that an MDR reportable event associated with the device constituent part of the combination product necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. This section also allows FDA to make written requests for the submission of all subsequent events of the same nature that involve substantially similar devices or device constituent parts of a combination product for the time period specified in the written request. This section only applies to reporters who would not otherwise submit a ''5-day report'' under the requirements associated with the application used to approve/clear the combination product with the device constituent part. Reporters must also maintain a record of any report they submit under this provision.

Proposed § 4.103(b)(2) requires reporters for combination products comprised of a device constituent part to report no later than 30 calendar days after the day the reporter becomes aware of information that reasonably suggests the device constituent part of the combination product has malfunctioned and that this device constituent part or a similar device constituent part that the reporter markets would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. This section only applies to reporters who would not otherwise submit a 30-day ''malfunction report'' under the requirements associated with the application used to approve/clear the combination product with the device constituent part. Reporters must also maintain a record of any report they submit under this provision.

Proposed § 4.103(b)(3) requires reporters for combination products comprised of a drug or a biological product constituent part to report each adverse experience associated with the use of the drug or biological product constituent part of the combination product that is both serious and unexpected, whether foreign and domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the sponsor. This section only applies to reporters who would not otherwise submit a ''postmarketing 15-day 'Alert report''' under the requirements associated with the application used to approve/clear the combination product with the drug or biological product constituent part(s). Reporters must also maintain a record of any report they submit under this provision.

Proposed § 4.103(b)(4) requires reporters for combination products comprised of a drug constituent part to report information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the drug constituent part of a distributed contribution product, or any failure of one or more distributed batches of the drug constituent part of a combination product to meet the specification established for it in its marketing application. Reporters must submit this information to the FDA district office that is responsible for the facility involved within 3 working days of its receipt. They must provide the information by telephone or other rapid communication means, with prompt written followup. This section only applies to reporters who would not otherwise submit a 3-day ''field alert report'' under the requirements associated with the application used to approve/clear the combination product with the drug product constituent part. Reporters must also maintain a record of any report they submit under this provision.

Proposed § 4.103(b)(5) requires reporters for combination products comprised of a biological product constituent part containing blood or a blood component, if a complication of blood collection or transfusion is confirmed to be fatal as described in § 606.170(b), to report by telephone, facsimile, express mail or electronically transmitted mail as soon as possible, and a written report within 7 days after the fatality. This section only applies to reporters who would not otherwise report such an event within this timeframe under the statutory provisions and regulatory requirements associated with the application used to approve/clear the combination product with the biological product constituent part containing blood or a blood component. Reporters must also maintain a record of any report they submit under this provision.

Information Collection Burden Estimate

FDA estimates the burden for this information collection as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN FOR HUMAN DRUGS[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
4.103(b)(1)	5	1	5	1	5
4.103(b)(2)	20	15	300	1	300
4.103(b)(3)	20	15	300	1	300
4.103(b)(4)	5	1	5	1	5
4.103(b)(5)	5	1	5	1	5
Totals	55		615		615

TABLE 2.—ESTIMATED ANNUAL POSTMARKETING SAFETY RECORDKEEPING BURDEN FOR COMBINATION PRODUCTS[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
4.103(b)(1)	5	1	5	.5	2.5
4.103(b)(2)	20	15	300	.5	150

TABLE 2.—ESTIMATED ANNUAL POSTMARKETING SAFETY RECORDKEEPING BURDEN FOR COMBINATION PRODUCTS[1]—Continued

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
4.103(b)(3)	20	15	300	.5	150
4.103(b)(4)	5	1	5	.5	2.5
4.103(b)(5)	5	1	5	.5	2.5
Totals	55		615		307.5

Burden

Based on FDA's experience regarding receipt of postmarketing safety reports for combination products, the agency estimates that there will be 55 reporters (who will keep corresponding records) submitting a total of 615 reports under proposed 4.103(b) annually (and maintaining the records of those reports). In other words, the agency estimates that there will be 55 reporters who will avail themselves of these new streamlined reporting requirements and benefit from the associated burden reductions. For example, manufacturers of drug-device combination products marketed under an NDA will now be able to submit postmarket safety reports following the requirements for drug products and no longer have to submit additional postmarket safety reports following the requirements for devices so long as they comply with the reporting and recordkeeping requirements of sections 4.103(b)(1) and 4.103(b)(2).

Further, FDA estimates, based on its experience with information collection regarding postmarketing safety reporting provisions for drugs, biological products, and devices, that each report will take approximately 1 hour to prepare and submit, and half an hour to fulfill the corresponding recordkeeping requirements.

FDA believes that there are no significant operating and maintenance costs associated with this collection of information because, in order to legally market their products, reporters are required to develop and maintain systems for reporting and maintaining records of postmarketing safety events. Therefore, appropriate mechanisms for postmarketing safety reporting should already be in place, and reporters will accrue no significant additional costs to fulfill the requirements set forth here.

We welcome comments on our estimates of the number of respondents who will avail themselves of the new streamlined reporting requirements and our burden estimates. Based on these comments, we will revise our estimates accordingly of the burden reductions associated with the reporting and recordkeeping requirements of §§ 314.80, 314.81, and 600.80, 600.81, 606.170, 803.20, and 803.53.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review.

The information collection provisions of the proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding information collection by November 2, 2009, to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Desk Officer, FAX: 202–395–6974.

VI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive Order requires agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under Federal statutes.'' The sole statutory provision giving preemptive effect to the proposed rule is section 751 of the act (21 U.S.C. 379r), which would apply only with respect to OTC drug components of combinations.[6]

[6] The proposed rule seeks to clarify which adverse event reporting 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 act applicable to prescription drugs or biological products. Section 521 of the act (51 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.

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies 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). In accordance with Executive Order 12866, FDA has carefully analyzed the economic effects of this proposal and has determined that the final rule, if issued, will not be a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule clarifies existing requirements and will have no recurring impact on the majority of small firms, the agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''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 $133 million, using the most current (2008)

Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. The Rationale Behind This Proposed Rule

The purpose of the proposed rule is to codify the postmarketing safety reporting requirements for combination products to ensure their consistent and appropriate regulation. The current regulations and reporting standards for drugs, devices, and biological products are similar but each has certain unique requirements. A separate rule specific to combination products will clarify how to apply these provisions to combination products and avoid applying duplicative or unnecessary requirements. The proposed rule will benefit public health by helping to ensure that the necessary reports are submitted and directed to the appropriate center and that records are maintained for the appropriate length of time.

C. Impact of Proposed Rule

The proposed rule will affect all of the approximately 300 manufacturers of combination products. Industry should benefit from reduced uncertainty regarding how to apply the separate regulations to combination products and from more consistent enforcement across the agency. This is especially true for developing standard operating procedures (SOPs) for new combination products. All firms would incur one-time costs to assess their current compliance level to the proposed requirements. In addition, some firms may need to alter or add SOPs and recordkeeping practices. Estimating the one-time costs is problematic because the costs would vary depending on the size of the firm, their current business practice, and the number and nature of their products. Currently we cannot identify how many combination products there are or the extent of the changes that would be needed. Some firms could spend as little as 30 minutes while other firms with a variety of combination product types, may have to alter or add a number of SOPs. This could take 10 to 20 hours per SOP.

The reporting requirements under proposed § 4.103(b) will also generate some annually recurring costs. Because all of the firms have reporting systems in place and the reports are submitted on the same form as the other types of postmarket safety reports (with the exception of field alert reports (proposed § 4.103(b)(4)), we estimate that the incremental time to comply with this requirement is about 1.5 hours and that we would receive about 615 reports from 55 firms annually. Assuming an hourly wage plus benefit rate of $42,[7] the annually recurring cost for these requirements would be $38,745 (1.5 hours x $42/hr x 615 reports). These costs could be at least partly offset because some of the proposed reports would be submitted in lieu of an existing reporting requirement.

About 80 to 85 percent of the firms affected by this proposed rule are considered small, based on the Small Business Administration's definition of a small entity (500 employees for medical device and biological product firms and 750 employees for drug firms). Most of these small entities are medical device firms and produce combination products where the primary modes of action are attributable to medical devices. The impact on individual firms will depend on the nature of the changes to SOPs needed, the number and type of combination products produced, and the number of reports filed annually. Most products will not have any postmarket safety reports in a given year and thus there would be no annually recurring costs for them. The largest potential cost would be a one-time cost to modify existing SOPs. The cost to make such modifications is generally lower for small firms than for large firms.

VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

The agency is proposing that any final rule that may issue based upon this proposed rule become effective 180 days after its date of publication in the **Federal Register**.

[7] Wage is based on the 2007 Bureau of Labor Statistic's survey, National Industry Specific Occupational Employment and Wage Estimate, for standard occupational code 13–1041, compliance officer in pharmaceutical and medicine manufacturing (NAICS 325400). The mean wage of $30.08 was increased by 40 percent to account for fringe benefits for a loaded wage of $42 per hour. *http://www.bls.gov/oes/current/naics4_325400.htm#b23-0000.*

List of Subjects in 21 CFR Part 4

Combination products, Biological products, Devices, Drugs, and Human cell, tissue, and cellular and tissue-based products, Regulation of combination products.

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, it is proposed that 21 CFR part 4 be further amended as proposed to be added at 73 FR 48430, September 23, 2009 as follows:

PART 4—REGULATION OF COMBINATION PRODUCTS

1. Add subpart B to part 4 to read as follows:

Subpart B—Postmarketing Safety Reporting for Combination Products

General Provisions

Sec.

4.100 What is the scope of this subpart?
4.101 What are the definitions applicable to this subpart?
4.102 Who reports to FDA?
4.103 What are the reporting requirements?
4.104 How do I report if another reporter is responsible for a constituent part of my combination product?
4.105 How, where, and when do I submit postmarketing safety reports for combination products?
4.106 What are the postmarketing safety reporting recordkeeping requirements?

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.

§ 4.100 What is the scope of this subpart?

(a) This subpart establishes requirements for postmarketing safety reporting for combination products.

(b) This subpart applies to the configurations of combination products described in § 3.2(e)(1), (e)(2), and (e)(3) of this chapter. This subpart does not apply to investigational combination products as defined in § 3.2(e)(4) of this chapter.

(c) This subpart applies to all reporters required to report under parts 314, 600, 606, and 803 of this chapter, except for user facilities and device distributors as defined in part 803 of this chapter.

(d) 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.

§ 4.101 What are the definitions applicable to this subpart?

Act means the Federal Food, Drug, and Cosmetic Act.

Adverse experience, as described in §§ 310.305(b), 314.80(a), and 600.80(a) of this chapter and as modified for purposes of this subpart, means any adverse event associated with the use of a drug or biological product constituent part of a combination product in humans, whether or not considered drug or biological product related, including the following: An adverse event occurring in the course of the use of a drug or biological product in professional practice, an adverse event occurring from drug or biological product overdose whether accidental or intentional, an adverse event occurring from drug or biological product abuse, an adverse event occurring from drug or biological product withdrawal, and any failure of expected pharmacological action.

ANDA means abbreviated new drug application as defined at § 314.3(b) of this chapter.

Application, for purposes of this subpart, means a new drug application, an abbreviated new drug application, a device premarket approval application, a device premarket notification submission, a humanitarian device exemption application, and/or a biologics license application, including all amendments and supplements to them.

Biological product has the meaning set forth in § 3.2(d) of this chapter.

BLA means biologics license application as described in section 351 of the Public Health Service Act (42 U.S.C. 262) and § 601.2 of this chapter.

Blood as defined in § 606.3(a) of this chapter means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

Blood component as defined in § 606.3(c) of this chapter means a blood component or part of a single-donor's blood separated by physical or mechanical means.

Blood fatality report means the report described in § 606.170 of this chapter of a complication of blood collection or transfusion confirmed to be fatal, by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible, and a written report within 7 days after the fatality.

Combination product has the meaning set forth in § 3.2(e) of this chapter.

Constituent part is a drug, device, or biological product that is part of a combination product as defined in § 3.1(e) of this chapter.

Device has the meaning set forth in section 201(h) of the act (21 U.S.C. 321(h)).

Drug has the meaning set forth in § 3.2(g) of this chapter.

FDA means the Food and Drug Administration.

Field alert report, as described in § 314.81(b)(1) of this chapter and as modified for purposes of this subpart, means a report submitted on Form FDA 3331 within 3 working days to the appropriate FDA district office when there is information concerning any incident that causes the drug constituent part of a distributed combination product or its labeling to be mistaken for, or applied to, another article; or that contains information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the drug constituent part of a distributed combination product, or any failure of one or more distributed batches of a drug constituent part of a combination product to meet the specification established for it in the application.

5-day report, as described in §§ 803.3 and 803.53 of this chapter and as modified for purposes of this subpart, means a medical device report (MDR) that must be submitted by a reporter to FDA under § 803.53(a) of this chapter no later than 5 work days after the day the reporter becomes aware that a MDR reportable event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. FDA can also make a written request for a 5-day report for all subsequent events of the same nature that involve substantially similar devices or device constituent parts of a combination product for the time period specified in the written request.

Followup report as described in §§ 314.80(c)(1)(ii), 600.80(c)(1)(ii), and 803.56 of this chapter and as modified for purposes of this subpart, is a report of supplemental, additional or followup information related to a reportable event.

HDE means humanitarian device exemption as discussed in § 814.100 of this chapter.

Malfunction, as described in § 803.3 of this chapter and as modified for purposes of this subpart, means the failure of a device constituent part of a combination product to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the combination product. The intended performance of a device constituent part refers to the intended use or indication for which the combination product is labeled or marketed.

Malfunction report, as required under section 227 of FDAAA, as described in § 803.20(b)(3)(ii) of this chapter, and as modified for purposes of this subpart, is a report submitted no later than 30 calendar days after the day that the reporter becomes aware of information that reasonably suggests that one of the marketed device constituent parts of a combination product has malfunctioned and that the device constituent part or a similar device or device constituent part of a combination product marketed by the reporter would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. A reporter must submit a 30-day malfunction report for malfunctions of the following devices: A Class III device; a Class II device that is permanently implantable, life supporting, or life sustaining; or a type of device that FDA, by notice in the **Federal Register** or letter, indicates should be subject to part 803 of this chapter to protect the public health. For Class I and certain Class II devices a reporter must submit reportable malfunctions on a quarterly basis using a summary format.

MDR means a medical device report as defined in § 803.3 of this chapter.

MDR reportable event, as described in § 803.3 of this chapter and as modified for purposes of this subpart, means an event about which the reporter has received or become aware of information that reasonably suggests that one of their marketed combination products:

(1) May have caused or contributed to a death or serious injury; or

(2) Has malfunctioned and that the device constituent part or a similar device or device constituent part of a combination product marketed by the reporter would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

NDA means new drug application as defined in § 314.3(b) of this chapter.

PMA means a device premarket approval application as defined in § 814.3 of this chapter.

Postmarketing 15-day ''alert report,'' as described in §§ 314.80(c)(1) and 600.80(c)(1) of this chapter and as modified for the purposes of this subpart, is a report the reporter must make to FDA for each adverse experience as defined in this subpart that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the reporter.

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

Reportable event, for purposes of this subpart, is an event that is reportable under this subpart or parts 314, 600, 606, or 803 of this chapter.

Reporter, for purposes of this subpart, is any person or entity responsible for evaluating and determining whether an event meets the criteria for postmarketing safety reporting or who is required to submit or record a reportable event under this subpart or parts 314, 600, 606, or 803 of this chapter. This term is used interchangeably with the term ''you.'' This term does not include user facilities or device distributors as defined in part 803 of this chapter.

Serious adverse experience, as described in §§ 314.80(a) and 600.80(a) of this chapter and as modified for purposes of this subpart, is any adverse experience occurring at any dose associated with the use of a drug or biological product constituent part of a combination product that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Serious injury means the injuries that are defined in § 803.3 of this chapter. This means an injury or illness that:

(1) Is life-threatening,

(2) Results in permanent impairment of a body function or permanent damage to a body structure, or

(3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Unexpected adverse experience, as described in §§ 314.80(a) and 600.80(a) of this chapter and as modified for the purposes of this subpart, means any adverse experience as defined in this subpart that is not listed in the current labeling for the combination product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity.

We means FDA.

§ 4.102 Who reports to FDA?

Any person or entity required to submit to FDA postmarketing safety reports for a combination product under parts 314, 600, 606, or 803 of this chapter must report under this subpart. This subpart uses the term ''reporters'' to refer to persons or entities responsible for evaluating and determining whether an event meets the criteria for postmarketing safety reporting or who are required to submit or record a reportable event. Additionally, the term ''you'' as used in this subpart refers to reporters. This subpart does not apply to user facilities or device distributors subject to medical device reporting as defined in part 803 of this chapter.

§ 4.103 What are the reporting requirements?

(a) *General requirements*. You must consider each of the following reporting requirements and comply with each that is applicable to your combination product or your constituent part(s), if another reporter is responsible for the other constituent part(s) of the combination product. If you are the only reporter for the combination product, you must consider the combination product as a whole (i.e., all of its constituent parts), when determining whether an event is required to be reported.

(1) If your combination product or your device constituent part is approved under a PMA or HDE, or is cleared under a premarket notification, you must comply with the requirements for postmarketing safety reporting described in part 803 of this chapter with respect to that combination product or device constituent part.

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

(3) If your combination product or your biological product constituent part is approved 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 that combination product or biological product constituent part.

(4) If your combination product or your device constituent part is not subject to a marketing application under the device provisions of the act because it was legally marketed prior to May 28, 1976, or is exempt from premarket notification, you must comply with the requirements for postmarketing safety reporting described in part 803 of this chapter with respect to that combination product or device constituent part.

(b) *Additional requirements*. If you are the only reporter for the combination product, depending on the type of combination product and the nature of the reportable event, you must submit, as applicable, the following additional reports and any associated followup reports. You must submit these additional reports only if the reports are not otherwise required to be reported by you under paragraph (a) of this section, or would be required, but at a later timeframe than specified as follows:

(1)(i) If your combination product contains a device constituent part, you must submit a ''5-day report'' no later than 5 work days after the day that you become aware that:

(A) An MDR reportable event associated with the use of the device constituent part of your combination product necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. You may become aware of the need for remedial action from any information, including any trend analysis; or

(B) We have made a written request for the submission of a 5-day report. If you receive such a written request from us, you must submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices or device constituent parts of a combination product for the time period specified in the written request. We may extend the time period stated in the original written request if we determine it is in the interest of the public health.

(ii) You must also submit any required followup reports to a ''5-day report'' required by § 803.56 of this chapter.

(2) If your combination product contains a device constituent part, you must submit a ''malfunction report'' no later than 30 calendar days after the day that you become aware of information that reasonably suggests the device constituent part, described in this paragraph, of your combination product has malfunctioned and that this device constituent part or a similar device or device constituent part that you market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. You must submit a 30-day malfunction report for reportable malfunctions of the following devices: A Class III device; a Class II device that is permanently implantable, life supporting, or life sustaining; or a type of device that FDA, by notice in the **Federal Register** or letter, indicates

should be subject to part 803 of this chapter to protect the public health. For Class I and certain Class II devices you must submit reportable malfunctions on a quarterly basis using a summary format. You must also submit any required followup reports to a ''malfunction report'' required by § 803.56 of this chapter.

(3) If your combination product contains a drug or a biological product constituent part, you must submit a postmarketing 15-day ''alert report'', for each adverse experience associated with the use of a drug or biological product constituent part of the combination product, whether or not considered drug or biological product related, that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the reporter, as required by § 314.80(c)(1)(i) or § 600(c)(1)(i) of this chapter. You must also promptly investigate and submit any required followup reports to a postmarketing 15-day ''alert report'' as required by § 314.80(c)(1)(ii) or § 600(c)(1)(ii) of this chapter.

(4) If your combination product contains a drug constituent part, you must submit a field alert report within 3 working days of your receipt to the FDA district office that is responsible for the facility involved, by telephone or other rapid communication means and prompt written followup, information concerning:

(i) Any incident that causes the drug constituent part of a distributed combination product or its labeling to be mistaken for, or applied to, another article; or

(ii) Any bacteriological contamination or any significant chemical, physical, or other change or deterioration in the drug constituent part of a distributed combination product, or any failure of one or more distributed batches of a drug constituent part of a combination product to meet the specification established for it in the application.

(5) If your combination product contains a biological product constituent part containing blood or a blood component, and a complication of blood collection or transfusion is confirmed to be fatal as described in § 606.170(b) of this chapter, you must submit a blood fatality report by telephone, facsimile, express mail, or e-mail as soon as possible, and a written report within 7 days after the fatality.

(c) *Periodic reports.* (1) If your combination product is approved under an NDA, ANDA, or BLA, you must also include information in reports submitted in accordance with paragraphs (b)(1), (b)(2), and (b)(5) of this section in the periodic reports you submit under §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(a) of this chapter. Information on these additional reports should be treated as 15-day alert reports, i.e., included in narrative summary and analysis of the information in the report and an analysis of the 15-day alert reports submitted during the reporting interval (all 15-day alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA). The history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated) should include information on the combination products as a whole (i.e., all of its constituent parts).

(2) If your combination product is approved under a PMA, you must also include information in reports submitted in accordance with paragraphs (b)(3), (b)(4), and (b)(5) of this section in the periodic reports you submit under §814.82(a)(7) of this chapter.

§ 4.104 How do I report if another reporter is responsible for a constituent part of my combination product?

(a) If another person holds an application used to approve or clear a constituent part of your combination product, or legally markets a constituent part of your combination product without an approved or cleared marketing application, in addition to the requirements of § 4.103(a), you must submit the information you received about the event to FDA or the other person within 5 calendar days of your receipt of the information.

(b) If you receive information from the other person that holds an application used to approve or clear a constituent part of your combination product, or legally markets a constituent part of your combination product without an approved or cleared marketing application, you must investigate and, if required, report the event in accordance with § 4.103(a) and (b).

§ 4.105 How, where, and when do I submit postmarketing safety reports for combination products?

(a) You must submit the field alert reports described in § 4.103(b)(4) to the FDA district office that is responsible for the facility involved within 3 working days of receipt of the information.

(b) You must submit all other postmarketing safety reports required under this subpart (i.e., required under § 4.103(a), (b)(1), (b)(2), (b)(3), (b)(5), and (c)) using the submission methods and timeframes identified in the regulations applicable under § 4.103(a), (b), and (c) for your combination product or your constituent part.

§ 4.106 What are the postmarketing safety reporting recordkeeping requirements?

(a) You must maintain records of postmarketing safety reports required by § 4.103(a) in accordance with the recordkeeping requirements of the underlying regulation(s) identified in § 4.103(a) that are applicable to your combination product or your constituent part.

(b) You must maintain records of reportable events required by § 4.103(b) and (c) for the time period specified as follows:

(1) 5-day and malfunction reports described in § 4.103(b)(1) and (b)(2): for 2 years or the expected life of the combination product, whichever is longer;

(2) Postmarketing 15-day 'alert reports' field alert reports, and blood fatality reports described in § 4.103(b)(3), (b)(4), and (b)(5), and periodic reports as described in § 4.103(c): for 10 years.

Dated: September 24, 2009.

David Horowitz,

Assistant Commissioner for Policy.

[FR Doc. E9–23519 Filed 9–30–09; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG–139068–08]

RIN 1545–BI31

Modification to Consolidated Return Regulation Permitting an Election To Treat a Liquidation of a Target, Followed by a Recontribution to a New Target, as a Cross-Chain Reorganization; Correction

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Correction to a notice of proposed rulemaking by cross-reference to temporary regulations.

SUMMARY: This document contains corrections to a notice of proposed rulemaking by cross-reference to temporary regulations (REG–139068–08) that were published in the **Federal Register** on Friday, September 4, 2009 (74 FR 45789) modifying the election under which a consolidated group can avoid immediately taking into account