POSTMARKETING SAFETY REPORTING FOR COMBINATION PRODUCTS
Final Rule
RIN 0910-AF82

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary/Legal Basis

In recognition of the growing number and significance of combination products to public health, 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. In further recognition of the increasing importance of this category of products and the complexity of their development and regulation, the 21st Century Cures Act of 2016 included amendments to section 503(g) to help further ensure an efficient, consistent and predictable regulatory pathway and program for them.

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 after being brought to market. 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).

Concerns expressed by external stakeholders about the lack of concrete information regarding the postmarketing safety reporting regulatory requirements for combination products, informed the decision to publish a proposed rule in 2009. Calls by stakeholders for the Agency to make finalization of that rule, with some clarifications, a priority prompted FDA to identify publication of the final rule as a key goal for 2016.

Some 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). Others have attempted to make reports in accordance with the PMSR requirements associated with each constituent part of the combination product. However, if, for example, the device constituent part of a drug-device combination product

marketed under NDA malfunctions and this could lead to serious injury or death, the reporter currently has no clear regulatory procedure to follow for whether or how to report this problem.

This lack of regulatory clarity could lead to reporting that does not adequately capture safety signals for combination products as appropriate to consider such signals and take action as appropriate in response to them. Such information can be important not only to ensuring safety of the particular product at issue but also of other products that may include the same or similar articles. As a consequence, this lack of regulatory clarity could compromise the ability of FDA to make sound regulatory decisions and inform sound action by product applicants 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 and clarify requirements for reporters by avoiding duplicative reporting requirements, FDA issued the final rule to create 21 CFR part 4, subpart B to clarify postmarketing safety reporting requirements for combination products.[1]

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

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

For a biological product, section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) requires FDA to approve a BLA on the basis of a demonstration that the product is safe, pure, and potent (section 351(a)(2)(C) of the PHS Act). Section 351(a)

[1] 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.

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

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

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

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

ensure sufficient and appropriate ongoing assessment of the risks associated with combination products.

Descriptions of Information Collections

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

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

Specifically, the additional reporting requirements specified in this rule for combination product applicants, along with any associated follow-up reports, are: (1) Submission of a "5-day report" as described in § 803.53 if the combination product contains a device constituent part; (2) submission of a "malfunction report" as described in § 803.50 if the combination product contains a device constituent part; (3) submission of a "correction or removal report" as described in § 806.10 if the combination product contains a device constituent part; (4) submission of a "field alert report" as described in § 314.81 if the combination product contains a drug constituent part; (5) submission of a 15-day report as described in § 314.80 or § 600.80 if the combination product contains a drug or biological product constituent part, respectively; and (6) submission of a "BPDR" as described in §§ 600.14 and 606.171 if the combination product contains a biological product constituent part.

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

We note that the PMSR information collections for the PMSR regulations associated with drugs, biological products, and devices found in §§ 314.80, 314.81, 600.80, 600.81, 606.170, 606.171, 803.50, 803.53, 803.56, 806.10, and 806.20 have already been

approved and are in effect. The pertinent PMSR information collection provisions for § 314.80(c) and (e), as well as for § 314.81(b) are approved under OMB Control No. 0910-0001, OMB Control No. 0910-0230, and OMB Control No. 0910-0291. The information collection provisions for §§ 600.80 and 600.81 are approved under OMB Control No. 0910-0308. Those for § 606.170 are approved under OMB Control No. 0910-0116. Those for § 606.171 are approved under OMB Control No. 0910-0458. The information collection provisions for §§ 803.50, 803.53, and 803.56 are approved under OMB Control No. 0910-0291 and OMB Control No. 0910-0437. The information collection provisions for §§ 806.10 and 806.20 are approved under OMB Control No. 0910-0359.

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

This rule contains a new information collection that pertains to constituent part applicants. Specifically, section 4.103 of the rule, requires the constituent part applicants for a combination product to share with one another information they receive regarding an event associated with the use of the combination product that involves a death or serious injury as described in 21 CFR 803.3 or an adverse experience as described in 21 CFR 314.80(a). Constituent part applicants are required only to share whatever information they initially receive regarding the event. They are not required to analyze, investigate or organize the information or take any other actions beyond forwarding the information as received. No further follow-up with the other constituent part applicant(s) is required. These requirements apply solely to the constituent part applicants for the combination product (e.g., as opposed to other persons holding approved applications to market the same or similar products not as part of a combination product).

Such an expedited sharing of information is important to ensure timely, complete reporting with regard to adverse events that may have been brought to the attention of only one constituent part applicant for a combination product. Enabling each constituent part applicant to review in a timely manner the information related to the combination product enhances efficiency and thoroughness of reporting because each constituent part applicant evaluates the information with respect to its own constituent part and with regard to the reporting requirements applicable to that type of constituent part.

The rule also addresses what records constituent part applicants must retain regarding the information shared, stating that these records must be kept for the longest recordkeeping period required under the PMSR regulations applicable to that applicant's constituent part. This provision was included to provide these applicants appropriate clarity and

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

2. Purpose and Use of the Information Collection

This rule applies to "combination product applicants" and "constituent part applicants". If there is a single person holding the application(s) under which a combination product received marketing authorization that person is the combination product applicant for that combination product. If different people hold the applications for different constituent parts of a combination product (e.g., one holds the application for the drug constituent part, and one holds the application for the device constituent part of a drug-device combination product), those two people are the constituent part applicants for that combination product (there is no combination product applicant).

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

The rule ensures that applicants evaluate and provide information to the Agency as necessary and appropriate to expedite FDA's safety review and evaluation, and thereby enhance the ability of the agency and these applicants to address safety concerns in prompt and effective manner.

3. Use of Improved Information Technology and Burden Reduction

The reporters are free to use whatever method they wish, including automated, electronic, mechanical, other technological collection techniques, or other forms of information technology that enables them to submit required reports as required for the report type under Part 4. We believe that this collection of information can help to reduce the burden in those cases where a reporter, unsure of where to report an adverse event for a combination product, might submit duplicate reports to separate centers. The proposed rule makes clear where to report events and ensures that this type of duplicative reporting will not occur.

4. Efforts to Identify Duplication and Use of Similar Information

The rule does not represent a duplication of effort.

5. Impact on Small Businesses or Other 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 rule will not have a significant economic impact on a substantial number of small businesses.

6. Consequences of Collecting the Information Less Frequently

A reporter would only submit a report to FDA if an adverse event described in the final rule occurs. If such an adverse event occurs but is not reported to FDA, the agency would have incomplete or inconsistent information. This could compromise the agency's ability to make sound regulatory decision about product safety, and the ability of the agency and applicants to take appropriate action to address safety concerns, and could jeopardize the public health.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

No special circumstances are associated with the collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

FDA participated in numerous public stakeholder meetings in which stakeholders have expressed concern about the lack of concrete information regarding the postmarketing safety reporting regulatory requirements for combination products. These stakeholders asked that FDA issue a rule on this topic to ensure consistent postmarketing safety reporting, and they have asked that the rule ensures that reporters do not have to submit duplicate reports. The agency also considered comments on the proposed rule (74 FR 50744, October 1, 2009) and other feedback from stakeholders regarding the importance of finalizing the rule to enable applicants to develop necessary safety systems, and ways in which to clarify the proposed rule, including with respect to entities subject to it. What requirements under the rule apply to which entities, and how to comply with those requirements. This final rule addresses stakeholder concerns by providing a consistent, predictable and streamlined mechanism to comply with postmarketing safety reporting requirements for combination products.

9. Explanation of Any Payment or Gift to Respondent

No payment or gifts are associated with this collection of information.

10. Assurance of Confidentiality Provided to Respondents

All information obtained by the agency will be reviewed in accordance with the guidelines set forth in the FDA Freedom of Information Regulations (21 CFR Part 20).

11. Justification for Sensitive Questions

This information collection does not contain questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

FDA estimates the total annual reporting and recordkeeping burden to be 12,885 hours as detailed in the tables below:

Table 1.—Estimated Annual Reporting Burden					
21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
4.102(c)(1)(i) Submitting 5-day reports	15	98	1,470	1.21	1,779
4.102(c)(1)(ii) Submitting malfunction reports	15	98	1,470	1.21	1,779
4.102(c)(1)(iii) Submitting correction or removal reports	20	1	20	10	200
4.102(c)(2)(i) Submitting field alerts	92	10.8	994	8	7,949
4.102(c)(2)(ii) and (3)((ii) Submitting 15-day reports	1	1	1	1	1
4.102(c)(3) Submitting BPDRs	24	6	144	2	288
4.102(d)	1	1	1	1	1
Totals					11,997

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

Table 3.—Estimated Annual Third Party Disclosure Burden					
21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
4.103 Sharing information with other constituent part applicants	33	18	594	.35	208

Based on FDA's experience regarding receipt of postmarketing safety reports for combination products, the agency estimates that there will be 401 reporters (who will keep corresponding records) submitting a total of 11,997 reports annually under 4.102(c) and (d) and 33 reporters (who will keep corresponding records) sharing information eighteen times annually under 4.103. Further, FDA estimates, based on its experience with information collection regarding postmarketing safety reporting provisions for

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

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

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

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

13. Estimates of Other Total Annual Costs to Respondents and Recordkeepers/Capital Costs

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, applicants 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.

14. Annualized Cost to the Federal Government

This collection of information will not lead to any significant costs to the Federal government. FDA will be reviewing reports received and taking action in response to them, but these activities are ongoing, and the overall volume of such reports and actions for medical product sis not anticipated to change significantly as a result of this rule.

15. Explanation for Program Changes or Adjustments

The information-sharing requirement for which OMB approval is being sought is a new collection arising from the final on postmarketing safety reporting requirements for combination products.

16. Plans for Tabulation and Publication and Project Time Schedule

We have no plans to tabulate or publish this collection of information.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

We believe that display of the OMB expiration date is appropriate for this collection of information.

18. Exceptions to Certification for Paperwork Reduction Act Submission

No exceptions to the certification statement have been identified.