SUPPORTING STATEMENT

PROPOSED RULE ON POSTMARKETING SAFETY REPORTING FOR COMBINATION PRODUCTS 0910-XXXX

A. Justification

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

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.[1]

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.

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[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.

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. It is crucial for the protection of the public health that these 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, 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.

2. Purpose and Use of the Information Collection

Any person required to submit or record a reportable event under 21 CFR §§ 310.305, 314, 600, 606, 803, except for user facilities and device distributors as defined in part 803 will collect this information. 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. This information will ensure the submission of necessary and appropriate information to expedite FDA's safety review and evaluation, and thereby enhance the agency's abilityt o protect and promote the public health.

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. 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 proposed 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 proposed 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 proposed 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 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. Efforts to Consult Outside the Agency

FDA has 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 have asked that FDA issue a proposed 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. This proposal addresses both those concerns

because it provides consistent postmarketing safety reporting requirements for combination products, while it also avoids duplicative reporting of those adverse events.

9. Payment/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. Sensitive Questions

This information collection does not contain questions of a sensitive nature (e.g., those regarding sexual behavior and attitudes, religious beliefs, etc.).

12. Estimates of Annualized Burden Hours and Costs

FDA estimates the total annual reporting and recordkeeping burden to be 924 hours as detailed in the tables below:

TABLE 1.--ESTIMATED ANNUAL POSTMARKETING SAFETY REPORTING BURDEN FOR COMBINATION PRODUCTS

21 CFR Section	Number 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

21 CFR Section	Number of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
4.103(b)(1)	5	1	5	.5	3
4.103(b)(2)	20	15	300	.5	150
4.103(b)(3)	20	15	300	.5	150
4.103(b)(4)	5	1	5	.5	3
4.103(b)(5)	5	1	5	.5	3
Totals	55		615		309

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). 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.

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,[2] 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.

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

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.

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 nor 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. Therefore, we estimate that each of the 300

[2] 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

manufacturers spend an average of 10 hours to alter or add SOPs. Assuming an hourly wage plus benefit rate of $42, this one-time cost would total $126,000 (300 manufacturers x 10 hours x $42/hr) or $420 per firm. In the proposed rule, we have asked for comments regarding these and other costs FDA has estimated. *(In order to ensure that this cost is indeed annualized, if approved, in OMB's burden tracking system, the total number of manufacturers estimated (300) was divided by 3 (years) to reach a total of 100 manufacturers. Therefore, the annualized, one-time cost is reported in the tracking system as $42,000).*

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.

14. Annualized Cost to the Federal Government

This collection of information will not lead to any costs to the Federal government.

15. Explanation for Program Changes or Adjustments

This is a new collection. FDA proposes to create 21 CFR part 4, subpart B to clarify 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.