Premarket Approval of Medical Devices
21 CFR Part 814
0910-0231

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting an extension of approval of the information collection requirements under 21 CFR Part 814.

Under section 515 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360(e)) all devices placed into class III by FDA are subject to premarket approval requirements. Premarket approval is the process of scientific and regulatory review to ensure the safety and effectiveness of class III devices. An approved PMA is, in effect, a private license granted to the applicant for marketing a particular medical device. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act (21 U.S.C. 351(f)) and cannot be marketed. Premarket approval requirements apply differently to preamendments devices, postamendments devices, and transitional class III devices.

Manufacturers of class III preamendments devices, devices that were in commercial distribution before May 28, 1976, are not required to submit a PMA until 30 months after the issuance of a final classification regulation or until 90 days after the publication of a final regulation requiring the submission of a PMA, whichever period is later. FDA may allow more than 90 days after issuance of a final rule for submission of a PMA.

A postamendments device is one that was first distributed commercially on or after May 28, 1976. Postamendments devices determined by FDA to be substantially equivalent to preamendments class III devices are subject to the same requirements as the preamendments devices. FDA determines substantial equivalence after reviewing an applicant's premarket notification submitted in accordance with section 510(k) of the FD&C Act. Postamendments devices determined by FDA to be not substantially equivalent to either preamendments devices or postamendments devices classified into class I or II are "new" devices and fall automatically into class III. Before such devices can be marketed, they must have an approved premarket approval application or be must reclassified into class I or class II.

The Food and Drug Modernization Act of 1997 (FDAMA) (Public Law 105-115), was enacted on November 21, 1997, to implement revisions to the FD&C Act by streamlining the process of bringing safe and effective drugs, medical devices, and other therapies to

the U.S. market. Several provisions affect the PMA process, and are further discussed throughout this supporting statement.

FDAMA added section 515(d)(6) to the FD&C Act (21 U.S.C. 360e(d)(6)), which provided that PMA supplements were required for all device changes that affect safety and effectiveness unless such changes are modifications to manufacturing procedures or method of manufacture. That type of manufacturing change will require a 30-day notice, or where FDA finds such notice inadequate, a 135-day PMA supplement.

The implementing regulations, contained in 21 CFR part 814, further specify the contents of a PMA for a medical device and the criteria FDA will employ in approving, denying, or withdrawing approval of a PMA and supplements to PMAs. The regulation's purpose is to establish an efficient and thorough procedure for FDA's review of PMAs and supplements to PMAs for class III medical devices. The regulations facilitate the approval of PMAs and supplements to PMAs for devices that have been shown to be reasonably safe and effective and otherwise meet the statutory criteria for approval. The regulations also ensure the denial of PMAs and supplements to PMAs for devices that have not been shown to be reasonably safe and effective and that do not otherwise meet the statutory criteria for approval.

Reporting Requirements:

21 CFR 814.15(b)
States that FDA will accept studies submitted in support of a PMA which have been conducted outside the United States and begun on or after November 19, 1986, if the data are valid and the investigator has conducted the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects. If the standards of the country are used, the applicant shall state in detail any differences between those standards and the "Declaration of Helsinki" and explain why they offer greater protection to the human subjects.

21 CFR 814.20
Specifies the information required in a PMA and update reports such as the applicant's name and address, a description of the device, its labeling, its indications for use, and summary of clinical and non-clinical studies.

21 CFR 814.37(a)-(c) and (e)
This specifies the procedures for amending an incomplete PMA or resubmitting a withdrawn PMA.

21 CFR 814.39(a), (c), (d) and (f) – Reporting
PMA supplements are required for all changes that affect safety and effectiveness unless such changes involve modifications to manufacturing procedures or method of manufacture. Changes to manufacturing procedures or methods which affect safety and effectiveness may require only a written notice to FDA, which describes the changes in

detail and summarize the information that supports the change. The devices subject to manufacturing changes can be distributed 30 days after a notification report is submitted to FDA unless the agency notifies the submitter that the notice is not adequate.

If the FDA deems the notice to be inadequate, FDA may request further information and require a 135-day PMA supplement.

FDA may require an applicant to submit new clinical data to demonstrate reasonable assurance of safety and effectiveness to support incremental changes.

21 CFR 814.82(a)(9)
Requires continued post-approval evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.

21 CFR 814.84(b)
Requires the holder of an approved PMA to submit periodic reports of new information related to the device (or related device) or changes in the device (or related device) that could affect its safety or effectiveness.

Recordkeeping Requirements:

21 CFR 814.82(a)(5) & (a)(6)
This requires maintenance of records that will enable the applicant to submit to FDA information needed to trace patients if necessary. It also requires maintenance of records for specified periods of time and organization and indexing into identifiable files to ensure the device's safety and effectiveness, to support continued approval of the device.

Expedited or Priority Review – Section 515(d)(5) of the FD&C Act
FDA will provide special review, which can include expedited processing of a Premarket Approval (PMA) application, for certain devices intended to treat or diagnose life threatening or irreversibly debilitating diseases or conditions. To receive special review, the devices must meet one of the following criteria:

1) The device represents a breakthrough technology;
2) There are no approved alternatives;
3) The use of the device offers significant advantages over existing approved alternatives; or
4) Availability is in the best interest of the patients.

Agreement Meeting – Section 520(g)(7) of the FD&C Act
Applicants planning to submit a Premarket Approval Application (PMA) may submit a written request to reach agreement with FDA on the key parameters of the investigational plan.

Determination Meeting – Section 513(a)(3)(D) of the FD&C Act
Applicants planning to submit a PMA may submit a written request to FDA for a meeting to determine the type of information (valid scientific evidence) necessary to support the effectiveness of their device.

Panel of Experts – Section 515(c)(3) of the FD&C Act
An original PMA or panel track PMA supplement is taken to an advisory panel of experts unless FDA determines that the information in the application substantially duplicates information which has previously been reviewed by the panel.

Day 100 Meeting – Section 515(d)(3) of the FD&C Act
FDA must, upon the written request of the applicant, meet with that party within 100 days of receipt of the filed PMA application to discuss the review status of the application. With the concurrence of the applicant, a different schedule may be established.

Prior to this meeting, FDA must inform the applicant in writing of any identified deficiencies and what information is required to correct those deficiencies. FDA must also promptly notify the applicant if FDA identifies additional deficiencies or of any additional information required to complete Agency review.

This information collection is not related to the American Recovery and Reinvestment Act of 2009 (ARRA).

2. Purpose and Use of the Information Collection

Respondents to the information collection are private sector, for-profit businesses.

The data reported to FDA and the records that are maintained by the applicants allow FDA and industry to make decisions and take actions to protect the public health from defective medical devices.

The PMA regulation establishes procedures that FDA utilizes in approving, denying, or withdrawing approval of any PMA. It provides specific, clear, and flexible instructions to applicants so those respondents know what information is required in a PMA. PMA supplements are also used by FDA to determine any additional action the agency must take to protect the public health.

3. Use of Improved Information Technology and Burden Reduction

Section 745A(b) of the FD&C Act, added by section 1136 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), provides statutory authority to require eCopies after issuance of final guidance (See Public Law No: 112-144). FDA's implementing guidance describes how device companies should replace one paper copy of a device application with an eCopy and identify the required format and technical requirements of the eCopy. The eCopy requirement does not require or request any information that is not already submitted to the Agency and/or covered under the existing ICR, and therefore does not change the cost or hour burden.

FDA estimates that 100% of the respondents will use electronic means to fulfill the agency's requirement or request.

4. Efforts to Identify Duplication and Use of Similar Information

FDA is the only Agency authorized to regulate the manufacture and distribution of medical devices. The information collected cannot be obtained from any other source other than the applicant, therefore this effort is not duplicated anywhere else. No similar data are available to or collected by FDA because each PMA is product and manufacturer specific. Most information in a PMA is unique and is presented to support claims of safety and effectiveness for that particular purpose.

5. Impact on Small Businesses or Other Small Entities

Respondents to this information collection are persons filing a PMA application or a PMA supplement with FDA for approval of certain class III medical devices. Based on User Fee payments, approximately 42 percent of PMA original application user fees were from small businesses. Approximately 4 percent of PMA supplement application user fees were from small businesses.

The efforts described below help to assure that the burden on all manufacturers, including small manufacturers, are minimized.

The Program Operations Staff (POS) in the Office of Device Evaluation (ODE), FDA, routinely participates in conferences and device submission workshops designed to educate the medical device industry on how to prepare a PMA submission such that it can be filed and reviewed in an expeditious manner. POS also annually meets with organizations such as Advanced Medical Technology Association (AdvaMed), Medical Device Manufacturers Association (MDMA), or Regulatory Affairs Professional Society (RAPS) to discuss issues regarding the PMA review process. FDA answers any questions that these organizations may have and provides them with information to improve their submissions. In addition, ODE also issues many device specific guidance documents and general guidance documents to assist the industry in improving the quality of their submissions.

FDA also maintains a fax on demand system (FACTS) which provides firms with information pertaining to medical devices and radiological health. FDA's Center for Devices and Radiological Health (CDRH), Division of International and Consumer Education (DICE) provides technical and non-technical assistance to small firms (and firms of any size) expressly to aid them in complying with requirements of the FD&C Act.

FDA also aids small business in dealing with the requirements of the regulations by providing guidance and information through the DICE, and through the scientific and administrative staff, and through the CDRH website at http://www.fda.gov/MedicalDevices/default.htm.

DICE participates in and presents conferences, workshops, and seminars on the application and interpretation of relevant regulations, consults with individual applicants, and develops and disseminates educational materials. Staff is available to respond to questions and a toll free telephone number was established to facilitate this communication link.

6. Consequences of Collecting the Information Less Frequently

Respondents will respond to the data collection annually and occasionally. Applicants determine when a product will be submitted for premarket approval. Notices and supplements are required only when an affected person or entity determines that a change that affects safety or effectiveness in their device is necessary. PMA applicants with approved PMAs are required to submit an annual report concerning their PMA. FDA determines subsequent reporting requirements and their frequency based on the necessity for applicants to provide reasonable assurance of their device's continued safety and effectiveness.

There are legal obstacles to reduce the burden as this collection is required by the FD&C Act and implementing regulations (21 CFR part 814). If this information were collected less frequently or, not collected, FDA could not ensure that the devices are reasonably safe and effective for their intended use.

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

Requirements under 5 CFR part 1320.5(d)(2) are met with an exception regarding the number of copies of information submitted. 5 CFR 1320.5 requires that not more than one original and two copies be submitted. FDA, however, requires under 21 CFR 814.20(b)(2) that each applicant must submit 6 copies of an [Original] PMA. Note that the requirement for 6 copies also applies to Panel Track Supplements. In addition, 21 CFR 814.39(c) requires 3 copies of a PMA supplement for review. Currently, PMA submission types must contain one (1) eCopy, one (1) paper copy, and the remaining copies of the applicant's choosing (eCopy or paper). FDA maintains all copies of the original PMA and PMA supplement in the Center for Devices and Radiological Health (CDRH)'s PMA Document Control Center until the eCopy of the submission is successfully loaded into the CDRH electronic document repository and the appropriate user fee is received (if applicable). The copies (paper or eCopy) of PMA's and PMA supplements are used for concurrent review by other personnel on the review team, such as the ODE Division, statisticians, GMP manufacturing inspection staff, Bioresearch Monitoring, or any review team member outside of CDRH .

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

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of 10/19/2016 (81 FR 72063). No comments were received.

The Program Operations Staff in the Office of Device Evaluation (ODE), FDA, annually meets with organizations such as Advanced Medical Technology Association

(AdvaMed), Medical Device Manufacturers Association (MDMA), or Regulatory Affairs Professional Society (RAPS) to discuss issues regarding the PMA review process.

9. Explanation of Any Payment or Gift to Respondents

There is no payment or gift provided to respondents of this information collection.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of data and disclosure regarding the existence of a PMA are governed by 21 CFR 814.9, the Freedom of Information Act (FOIA) (5 U.S.C. 552), and sections 301(j) and 520(c) and (h) of the FD&C Act (21 U.S.C. 331(j), 360(c) and (h)). Under FOIA, the public has broad access to government documents.

However, FOIA provides certain exemptions from mandatory public disclosure of government records (5 U.S.C. 552(b)(1)-(b)(9)). One such provision, 5 U.S.C. 552(b)(4), exempts "trade secrets and commercial or financial information that is privileged or confidential" from the requirement of public disclosure.

Section 520(c) of the FD&C Act prohibits FDA from disclosing any information exempted from public disclosure under 5 U.S.C. 552(b)(4). Part 20 of FDA's regulations (21 CFR part 20) sets forth FDA's general policy concerning public availability of FDA records. Under section 520(h) of the FD&C Act, FDA is required to make publicly available a detailed summary of the safety and effectiveness information contained in a PMA that is the basis for an order approving, denying approval of, or withdrawing approval of a PMA.

11. Justification for Sensitive Questions

The information required in a premarket approval or premarket supplement application does not include questions of a sensitive nature, such as, sexual behavior and attitudes, religious beliefs, and other matters that are commonly considered private.

12. Estimates of Annualized Burden Hours and Costs

12 a. Annualized Hour Burden Estimate

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden

Activity/21 CFR or FD&C Act Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Research conducted outside the United States (814.15(b))	25	1	25	2	50
PMA application (814.20)	35	1	35	668	23,380
PMA amendments and resubmitted PMAs (814.37(a)-(c) and (e))	1,222	1	1,222	167	204,074

Table 1.--Estimated Annual Reporting Burden					
Activity/21 CFR or FD&C Act Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
PMA supplements (814.39(a))	695	1	695	60	41,700
Special PMA supplement—changes being affected (814.39(d))	88	1	88	6	528
30-day notice (814.39(f))	1,710	1	1,710	16	27,360
Postapproval requirements (814.82(a)(9))	340	1	340	135	45,900
Periodic reports (814.84(b))	695	1	695	10	6,950
Agreement meeting (520(g)(7))	1	1	1	50	50
Expedited review request (515(d)(5) of the FD&C Act)	6	1	6	10	60
Determination Meeting (513(1)(3)(D) of the FD&C Act)	1	1	1	50	50
Panel meeting (515(c)(3) of the FD&C Act)	9	1	9	30	270
Day 100 meeting (515(d)(3) of the FD&C Act)	19	1	19	10	190
Total					350,562

Table 2.--Estimated Annual Recordkeeping Burden					
Activity/21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Maintenance of records (814.82(a)(5) and (a)(6))	422	1	422	17	7,174

The industry-wide burden estimate for PMAs is based on an FDA average fiscal year (FY) annual rate of receipt of PMA submissions data and our expectation of submissions to come in the next few years. The burden data for PMAs is based on data provided by applicants by device type and cost element in an earlier study.

Reporting Burden:
The reporting burden can be broken out by certain sections of the PMA regulation as follows:

§ 814.15(b)--Research Conducted Outside the United States
Each foreign study should be performed in accordance with the "Declaration of Helsinki" or the laws and regulations of the country in which the study was conducted. If the study was conducted in accordance with the laws of the country, the PMA applicant is required to explain to FDA in detail the differences between the laws of the country and the "Declaration of Helsinki". Based on the number of PMAs received that contained studies

from overseas, FDA estimates that the burden estimate necessary to meet this requirement is 50 hours.

§ 814.20 --Application

Included in this requirement are the conduct of laboratory and clinical trials as well as the analysis, review, and physical preparation of the PMA application. FDA estimates that 40 applicants, including hospital re-manufacturers of SUDs, will be affected by these requirements which are based on the actual average of FDA receipt of new PMA applications in FY 2010 through 2012. FDA's estimate of the hours per response (668) was derived through FDA's experience and consultation with industry and trade associations. In addition, FDA also based its estimate on the results of an earlier study that accounts for the bulk of the hourly burden for this requirement, which is identified by applicants.

§ 814.37(a) through (c) and (e)--PMA Amendments and Re-Submitted PMAs

As part of the review process, FDA often requests PMA applicant to submit additional information regarding the device necessary for FDA to file the PMA or to complete its review and make a final decision. The PMA applicant may, also on their own initiative, submit additional information to FDA during the review process. These amendments contain information ranging from additional test results, re-analysis of the original data set to revised device labeling. Almost all PMAs received by the agency have amendments submitted during the review process. FDA estimates that 204,074 burden hours are necessary to satisfy this requirement.

§ 814.39(a)--PMA Supplements

FDA believes that 41,700 hours of burden are needed to complete the requirements for the range of PMA supplements (180-day fee-based, 180-day non-fee based and real-time supplements).

§ 814.39(d)--Special PMA Supplements--Changes Being Affected

This type of supplements is intended to enhance the safety of the device or the safe use of the device. The number of PMA supplements received that fit this category averaged 80 per year based on the numbers received from FY 2010 through FY 2012. Because of the minimal data required to be included in this type of supplement, FDA estimates that the burden hours necessary to satisfy this requirement are 528 hours.

§ 814.39(f)--30-Day Notice

Under section 515(d) of the FD&C Act, modifications to manufacturing procedures or methods of manufacture that affect the safety and effectiveness of a device subject to an approved PMA do not require submission of a PMA supplement under paragraph (a) of this section and are eligible to be the subject of a 30-day notice. A 30-day notice shall describe in detail the change, summarize the data or information supporting the change, and state that the change has been made in accordance with the requirements of part 820 (21 CFR part 820). The applicant may distribute the device 30 days after the date on which FDA receives the 30-day notice, unless FDA notifies the applicant within 30 days

from receipt of the notice, that it is not adequate. FDA estimates the burden to satisfy this requirement is 27,360 hours.

§ 814.82(a)(9)--Post-Approval Requirements
Post-approval requirements concerns approved PMAs that were not reclassified and require a periodic report. After approval, all PMAs require a submission of an annual report. A majority of the submitted PMAs require associated post-approval studies, i.e., follow-up of patients used in clinical trials to support the PMA or additional preclinical information, that is labor-intensive to compile and complete; the remaining PMAs require minimal information. Based on experience and consultation with industry, FDA has estimated that preparation of reports and information required by this section requires 45,900 hours.

§ 814.84(b)--Periodic Reports
Post-approval requirements described in § 814.82(a)(7) require submission of an annual report for each approved PMA. FDA estimates that respondents will average about 10 hours in preparing their reports to meet this requirement. This estimate is based on FDA's experience and consultation with industry. Thus, FDA estimates that the periodic reporting burden required by this section will take 6,950 hours.

Recordkeeping:
§ 814.82(a)(5) and (a)(6)--Maintenance of records
The recordkeeping burden under this section requires the maintenance of records, used to trace patients and the organization and the indexing of records into identifiable files to ensure the device's continued safety and effectiveness. These records are required of all applicants who have an approved PMA

PMAs have been required since 1976, and there are 556 active PMAs that could be subject to these requirements, based on actual FDA data, and approximately 25 new PMAs are approved every year. The aggregate burden for the estimated 600 PMA holders of approved original PMAs for the next few years is estimated to be 7,174 hours.

The applicant determines which records should be maintained during product development to document and/or substantiate the device's safety and effectiveness. Records required by the current good manufacturing practices for medical devices regulation (part 820) may be relevant to a PMA review and may be submitted as part of an application. In individual instances, records may be required as conditions of approval to ensure the device's continuing safety and effectiveness.

12b. Annualized Cost Burden Estimate

FDA estimates that the total estimated burden cost to industry relating to this information collection will be $9,661,790, which is the total estimated number of burden hours, 158,390, multiplied by an average wage rate of $61 per hour.*

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Regulatory Affairs Professional*	357,736	$61	$21,821,896

* Based on The Regulatory Affairs Professional Society (RAPS) overall base annual compensation of $126,163 for a U.S. regulatory affairs professional (http://www.raps.org/news-trends/scope-of-practice/2014/). The hourly rate of $61 above assumes a 40-hour work week and is rounded to the nearest dollar.

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

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

FDA estimates that a total of 118 full time equivalent (FTE) positions are used for PMA review and processing. An average full time equivalent (FTE) employee is projected to cost FDA/CDRH $283,487,* which consists of the employee's salary and any overhead which accompanies that employee. The burden to government of this information collection is $33,451,466 per year ($283,487 x 118 FTEs).

*Based on the Department of Health and Human Services, Fiscal Year 2015, Food and Drug Administration, Justification of Estimates for Appropriations Committees--ALL PURPOSE table (pp. 11-13).

15. Explanation for Program Changes or Adjustments

The number of respondents for each IC has been adjusted to reflect current Agency data. The number of recordkeeping respondents has decreased from 607 to 422. As a result, the hourly burden estimate has decreased by 5,566 hours (previously 12,740 hours; now 7,174 hours).

Upon review of this ICR we have corrected the IC for "PMA amendments and resubmitted PMAs (814.37(a)-(c) and (e))" to include amendments to supplements, which were erroneously not included in the IC. This correction has caused the number of respondents for that IC to increase from 120 to 1,222, and the estimated burden for the IC to increase from 20,040 hours to 204,074 hours.

Additionally, we have adjusted the number of respondents to reflect current Agency data for all the reporting ICs. The total reporting burden estimate has increased by 2,759 respondents (previously 2,087; now 4,846) and 227,137 hours (previously 123,425 hours; now 350,562 hours).

The total burden estimate for the ICR has increased from 136,165 hours to 357,736 hours.

16. Plans for Tabulation and Publication and Project Time Schedule

    There are no plans to publish the collection of information under these regulations for statistical use unless requested by Congress in accordance with section 533 of the FD&C Act.

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

    Currently, FDA is not requesting an exemption for display of the OMB expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

    There are no exceptions to the certification.