U.S. Food and Drug Administration
Acceptance of Data from Clinical Investigations for Medical Devices
OMB Control No. 0910-0741
RIN 0910–AG48

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

Under section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360j(g)), the procedures and conditions that FDA[1] is authorized to prescribe for granting an investigational device exemption (IDE) include the requirement that an application be submitted to FDA, in such form and manner as the agency shall specify, and other requirements necessary for the protection of the public health and safety. Section 520(g) also requires that the information submitted in support of an IDE application be "adequate to justify the proposed clinical testing."

Section 515(c)(1)(A) of the FD&C Act (21 U.S.C. 360e(c)(1)(A)) requires that premarket approval (PMA) applications contain, among other information, full reports of all information, published or known to or which should reasonably be known to the PMA applicant, concerning investigations bearing on the safety or effectiveness of the device for which premarket approval is sought. Section 515(d)(2) of the FD&C Act (21 U.S.C. 360e(d)(2)) states that FDA shall deny approval of a PMA application if the Agency finds that "there is a lack of a showing of reasonable assurance that such device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof" or "there is a lack of a showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," among other reasons.

Under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), device manufacturers are required to submit a premarket notification (510(k)) to FDA before introducing or delivering for introduction into interstate commerce for commercial distribution a device, unless the device is exempt from premarket notification. FDA reviews a premarket notification submission to determine whether the device is substantially equivalent to a legally marketed (predicate) device. Under section 513(i) of the FD&C Act (21 U.S.C. 360c(i)), determinations of substantial equivalence include some inquiry into the comparable safety and effectiveness of the device, where appropriate. For devices that have the same intended use as the predicate device but different technological characteristics, information submitted to demonstrate substantial equivalence must include "appropriate clinical or scientific data[,] if deemed necessary" by the FDA,

[1] In light of section 1003(d) of the FD&C Act (21 U.S.C. 393(d)) and the Secretary of Health and Human Services' (the Secretary's) delegation to the Commissioner of Food and Drugs, statutory references to "the Secretary" have been changed to "FDA" or the "agency."

showing that "the device is as safe and effective as a legally marketed device" and "does not raise different questions of safety and effectiveness than the predicate device."

Under section 520(m) of the FD&C Act (21 U.S.C. 360j(m)), FDA may grant an humanitarian device exemption (HDE) if FDA finds that: The device is designed to treat or diagnose a disease or condition that affects not more than 8,000 individuals in the United States; the device would not be available to a person with such disease or condition unless FDA grants the exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition; and the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

Section 513(f)(2) of the FD&C Act (21 U.S.C. 360c(f)(2)) authorizes the submission of a request for *de novo* classification for a device for which there is no legally marketed device upon which to base a substantial equivalence determination, and authorizes FDA to classify the device subject to the request under the criteria set forth in section 513(a)(1) of the FD&C Act (21 U.S.C. 360c(a)(1)).

Section 569B of the FD&C Act (21 U.S.C. 360bbb-8b), which was added by the Food and Drug Administration Safety and Innovation Act (Pub. L. No. 112-144; 126 Stat. 1113) in 2012, requires FDA to accept data from clinical investigations conducted outside the United States, if the applicant demonstrates that such data are adequate under FDA's applicable standards to support clearance or approval of the device.

Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes the Agency to issue regulations for the efficient enforcement of the FD&C Act.

These statutory provisions authorize us to issue regulations describing when we may consider data from clinical investigations, whether conducted inside or outside the United States, as reliable evidence supporting an IDE, PMA, 510(k), PDP, request for *de novo* classification, or HDE application or submission. Whether data from an investigation involving human subjects support the application or submission depends, in part, on whether the investigation was conducted in accordance with ethical and other principles that provide assurance of the quality and integrity of clinical data and adequate protection of human subjects.

FDA is amending its regulations on acceptance of data from clinical investigations for medical devices. We are requiring that data submitted from clinical investigations conducted outside the United States intended to support an IDE application, a 510(k) submission, a request for *de novo* classification, a PMA application, a product development protocol (PDP) application, or a HDE application be from investigations conducted in accordance with good clinical practice (GCP), which includes obtaining and documenting the review and approval of the clinical investigation by an independent ethics committee (IEC) and obtaining and documenting freely given informed consent of

subjects, which includes individuals whose specimens are used in investigations of medical devices. The final rule titled "Human Subject Protection; Acceptance of Data from Clinical Investigations for Medical Devices" updates the criteria for FDA acceptance of data from clinical investigations conducted outside the United States to help ensure the protection of human subjects and the quality and integrity of data obtained from these investigations. As part of this final rule, we are also amending the IDE and 510(k) regulations to address the requirements for FDA acceptance of data from clinical investigations conducted inside the United States. The final rule provides consistency in FDA requirements for acceptance of data from clinical investigations, whatever the application or submission type.

While the information collections in this ICR are revisions to current approved information collections, these collections have been submitted to OMB as a new information collection request (assigned OMB control number 0910-0741, "Human Subject Protection; Data Requirements for Medical Device Related Clinical Investigations"), with the expectation that the currently approved requirements will be amended. As such the following collections of information will be amended and submitted to OMB for approval as revisions to currently approved information collections after the rule is finalized and the collections are due for renewal. The ICRs to be amended include: OMB control numbers 0910-0078, 0910-0120, 0910-0231, and 0910-0332. Upon approval of all the amendments, we will request discontinuance of this ICR (OMB control number 0910-0741, "Human Subject Protection; Data Requirements for Medical Device Related Clinical Investigations").

We are requesting approval for the following collections of information:

Section 807.87--Information Required in a Premarket Notification Submission (OMB Control No. 0910-0120, adds new reporting IC for § 807.87(j))

Section 807.87 is being amended to address requirements for 510(k) submissions supported by clinical data. For clinical investigations conducted in the United States, submitters will be required to submit a statement as described in § 807.87(j)(1). For clinical investigations conducted outside the United States, submitters will be required to submit the information as described in § 807.87(j)(2).

Section 812.27--Report of Prior Investigations (OMB Control No. 0910-0078, adds new reporting ICs for § 812.27(b)(4)(i) and (b)(4)(ii), respectively)

Section 812.27 is being amended to address requirements for IDE applications supported by clinical data. For clinical investigations conducted in the United States, sponsors will be required to submit a statement as described in § 812.27(b)(4)(i). For clinical investigations conducted outside the United States, sponsors will be required to submit the information as described in § 812.27(b)(4)(ii).

Section 812.28—Acceptance of Data from Clinical Investigations Conducted Outside the United States (OMB Control No. 0910-0078, adds new reporting ICs for § 812.28(a)(1), (b), and (c), respectively, and adds new recordkeeping IC for § 812.28(d))

Section 812.28 is being added to address the requirements for acceptance of foreign clinical data to support an IDE or a device marketing application or submission. The sponsor or applicant will be required to submit a statement as described in § 812.28(a)(1); provide a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP that includes the information in § 812.28(b)(1) through (b)(12) or a cross-reference to another section of the application or submission where the information is located; submit requests for waivers as described in § 812.28(c); and retain the records as described in § 812.28(d).

Section 812.140--Records Retention (OMB Control No. 0910-0078, adds new recordkeeping IC for § 812.140)

Section 812.140 is being amended to address record retention requirements for investigators and sponsors. An investigator or sponsor will be required to maintain records as described in § 812.140(d).

Section 814.20--Application (OMB Control No. 0910-0231, adds new reporting IC for § 814.20(b)(6)(ii))

Section 814.20 is being amended to address requirements for a PMA supported by data from clinical investigations conducted outside the United States. The applicant will be required to submit the information as described in § 814.20(b)(6)(ii)(C).

Section 814.104--Original Applications (OMB Control No. 0910-0332, adds new reporting IC for § 814.104(b)(4)(i))

Section 814.104 is being amended to address submission of data from clinical investigations in an HDE. To the extent the applicant includes data from clinical investigations, the applicant will be required to include the information and statements as described in § 814.104(b)(4)(i).

2. Purpose and Use of the Information Collection

The rule is intended to update the standards for FDA acceptance of data from clinical investigations conducted outside the United States and to help ensure the protection of human subjects and the quality and integrity of data obtained from these investigations. As part of this rule, we are also amending the IDE and 510(k) regulations to address the requirements for FDA acceptance of data from clinical investigations conducted inside the United States. The amendments are intended to provide consistency in FDA requirements for acceptance of clinical data, whatever the application or submission type. FDA believes that the requirements for FDA's acceptance of data from clinical investigations should be consistent regardless of the type of submission or application in which the data are submitted to FDA. For data from clinical investigations conducted inside the United States, we require statements in 510(k) submissions, HDE applications, and IDE applications that are similar to those required for PMA applications, to help ensure the protection of human subjects and the quality and integrity of data obtained from these investigations. For data from clinical investigations conducted outside the United States, FDA believes that revision of the requirements for FDA acceptance of data from these clinical investigations is needed for several reasons, such as updating standards for FDA acceptance of data from clinical investigations conducted outside of

the United States, ensuring the quality and integrity of such data, standardizing human subject protection, and providing consistency in FDA requirements for acceptance of clinical data from these investigations, whatever the application or submission type.

The rule requires additional maintenance, retention, and submission of documents indicating (1) clinical investigations conducted outside the United States and used to support IDE or device marketing applications or submissions are conducted in accordance with GCP, and (2) availability of data for FDA inspection, if deemed necessary.

The information allows reviewers to assess the appropriateness and adequacy of the clinical investigation design, data collection plans, conduct, and performance, and helps to protect human subjects participating in medical device clinical investigations.

3. Use of Improved Information Technology and Burden Reduction

Section 745A(b) of the FD&C Act (21 U.S.C. 379k-1(b)), added by section 1136 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) (Pub. L. No. 112-144; 126 Stat. 1124), provides statutory authority to require electronic copies (eCopies) of device applications, submissions, and presubmissions after issuance of final guidance. FDA's implementing guidance describes how device companies must replace all except for one paper copy of a device application, submission, or presubmission with an eCopy and meet the technical standards outlined in the guidance.

Therefore, FDA estimates that 100% of the respondents will use electronic means to fulfill the agency's requirements.

4. Efforts to Identify Duplication and Use of Similar Information

FDA is the only Federal agency responsible for the collection of information associated with acceptance of data from clinical investigations to support device research or marketing applications or submissions. No similar information is currently collected by any other agency and, therefore, no similar information is available that can be used or modified for the purpose described.

5. Impact on Small Businesses or Other Small Entities

The percentage of respondents that may be considered a small business is estimated to be 99%. Dunn & Bradstreet, Inc., data on the number of establishments by employee size for the year 2009 (used in the Regulatory Impact Analysis for the rulemaking) indicate that most of the establishments have employee sizes by which they would be considered small.

6. Consequences of Collecting the Information Less Frequently

The information will be collected when a company submits a submission or application for clearance or approval. Because manufacturers determine when a research or marketing application or submission for a product will be submitted for clearance or approval, the frequency of FDA's receipt of submissions and applications (and

information collections described in this supporting statement) will be determined by the frequency with which sponsors and applicants submit applications and submissions.

This information collection allows FDA to collect data and information in IDE applications to help ensure that the investigational device's use will not present an unreasonable risk for the subject enrolled in the investigation and will not violate the subject's rights. If the information was obtained less frequently, it would not be possible to assure protection of the public health from significant risk devices. There are no legal obstacles to reduce the burden.

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

Requirements under 5 CFR 1320.5(d)(2) are met with the 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) and 814.39(c)(1), respectively, that each respondent must submit 6 copies of a PMA application and 3 copies of a PMA supplement for review. Consequently, information pursuant to this information collection request that is to accompany a PMA application or supplement will be submitted in multiple copies. FDA maintains the original PMA application and PMA supplement in the PMA Document Control Center in its Center for Devices and Radiological Health (CDRH) until the submission is scanned and placed in the CDRH electronic document repository. Additional copies of PMA applications and PMA supplements are used for concurrent review by CDRH personnel such as the ODE Division, statisticians, GMP manufacturing inspection staff, and Bioresearch Monitoring. The final copy of a PMA application or PMA supplement is retained for team review by other statisticians, physicians, and scientists. FDA also requires under 21 CFR 812.20(a)(3) that each respondent must submit 3 copies of an IDE application for review.

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

The proposed rule, published in the Federal Register on February 25, 2013 (78 FR 12664), solicited comments on this information collection prior to its submission to the Office of Management and Budget (OMB). A discussion of the comments received and FDA's response can be found in the final rule "Human Subject Protection; Acceptance of Data from Clinical Investigations for Medical Devices." None of the comments addressed the information collection analysis specifically or necessitated changes to the burden analysis.

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 information submitted to FDA under a premarket notification is governed by the provisions of 21 CFR Part 20 and 807.95, and is mandated. However, the purpose of the 510(k) summaries or 510(k) statements submitted in a premarket

notification is to make information available to the public within 30 days if a device has been cleared for marketing through the 510(k) process.

Confidentiality of data and disclosure regarding the existence of a PMA or PDP application are governed by 21 CFR 814.9. Confidentiality of data and disclosure regarding the existence of an IDE are governed by 21 CFR 812.38. Section 814.122(a) states that any record in the HDE file, including all data and information submitted with or incorporated by reference into the HDE, any HDE supplement, any report under § 814.126, any master file, or any other related submission, will be available for public disclosure in accordance with the restrictions and conditions available to PMA files under § 814.9(b) through (h), and the public information regulations at 21 CFR Part 20.

These provisions do not permit disclosure of information in a premarket submission that is trade secret or commercial confidential unless that information has been previously disclosed or as permitted under the Federal Freedom of Information Act. Under the Freedom of Information Act (FOIA) (5 U.S.C. 552), the public has broad access to government documents.

11. Justification for Sensitive Questions

The information required does not include questions about sexual behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Burden Hours and Costs

12 a. Annualized Hour Burden Estimate

The following is the estimated annual burden hours for submitters to comply with the information collection requirements imposed by this regulation:

Table 1.—Estimated Annual Reporting Burden[1]

21 CFR Section/ Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
807.87(j)—Human subject protection statement and information in a premarket notification submission supported by clinical data	1,500	1	1,500	0.25 (15 minutes)	375
812.27(b)(4)(i)—Report of prior investigations; U.S.	400	1	400	1	400

Table 1.—Estimated Annual Reporting Burden[1]

21 CFR Section/ Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
812.27(b)(4)(ii)—Report of prior investigations; outside the U.S.	100	1	100	0.25 (15 minutes)	25
812.28(a)(1)—Data from clinical investigations[2]	1,500	1	1,500	0.25 (15 minutes)	375
812.28(b)—Description regarding GCP[2]	1,500	1	1,500	10	15,000
812.28(c)—Waivers[2]	10	1	10	1	10
814.20—Application information	10	1	10	0.50 (30 minutes)	5
814.104—Original applications statements and information	10	1	10	8	80
Total					16,270

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] No precise data is available for requests for de novo classifications. However, excluding these data from the analysis is not expected to impact the final estimate because the FDA tends to receive fewer requests for de novo classifications per year than HDE applications (including supplements).

Table 2.—Estimated Annual Recordkeeping Burden[1]

21 CFR Section/ Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
812.28(d)—records from clinical investigations conducted outside the U.S.[2]	1,500	1	1,500	1	1,500
812.140—Retention period	10	1	10	1	10
Total					1,510

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] No precise data is available for requests for de novo classifications. However, excluding these data from the analysis is not expected to impact the final estimate because the FDA tends to receive fewer requests for de novo classifications per year than HDE applications (including supplements).

The respondents to this information collection are domestic and foreign device sponsors or applicants. The total estimated burden imposed by these information collection requirements is 17,780 annual hours. FDA based the estimated number of respondents on

empirical data for 510(k), PMA, HDE, PDP, and IDE submissions and applications received by FDA. Time estimates for statements attesting each investigation was conducted in compliance with the applicable regulations or a statement describing the reason for noncompliance are based upon CDRH staff completing the statements.

12b. Annualized Cost Burden Estimate

The information collection consists of reporting and recordkeeping activities, which are expected to be conducted by occupations in the medical equipment and supplies industry (North American Industry Classification, NAICS, code 339100). Reporting activities are valued using median hourly wages for Natural Sciences Manager occupations (Standard Occupational Classification, SOC, 11-9121). According to the Bureau of Labor Statistics (BLS) May 2015 National Industry-Specific Occupational Employment and Wage Estimates[2], the median hourly wage for Natural Sciences Managers is calculated to approximately equal $64.23. To account for benefits and overhead, we double this value to $128.46. Recordkeeping activities are valued using median hourly wages for Office and Administrative Support occupations (SOC 43-0000). BLS calculates the median hourly wage for Office and Administrative Support to approximately equal $17.44. To account for benefits and overhead, we double this value to $34.88.

We believe the annual cost burden to the respondents for the reporting activities of this information collection will be $2,090,044 annually. ($128.46 * 16,270 hours = $2,090,044 (rounded)). We believe the annual cost burden to the respondents for the recordkeeping activities of this information collection to be $52,669 annually. ($34.88 * 1,510 hours = $52,669 (rounded)). As a result, we believe the total annual cost burden to the respondents for this information collection will be $2,142,713.

Type of Respondent	Burden Hours	Hourly Wage Rate	Total (rounded)
Natural Sciences Manager	16,270	$128.46	$2,090,044
Office and Administrative Support	1,510	$34.88	$52,669
Total Cost			$2,142,713

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

[2] Bureau of Labor Statistics. National Occupational Employment and Wage Estimates. Occupational Employment Statistics, May 2015. https://www.bls.gov/oes/current/naics4_339100.htm, accessed January 26, 2016.

The estimated annualized cost to the Federal Government is $83,130.

Activity	Number of Responses	Hours per Response	Cost per Hour	Total Cost
Clinical Study Reporting	6,540	0.25	$67.83	$110,902

The estimated time for review and data entry is 15 minutes, yielding a total of 1,635 hours for reviewing all responses. The information will be extracted by program personnel at a GS-14 salary cost of $67.83 (https://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/16Tables/html/DCB_h.aspx) per hour for a total cost to the Federal Government of $110,902 (rounded).

15. Explanation for Program Changes or Adjustments

This is a new information collection.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

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

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 Item 19 of OMB Form 83-I.