Acceptance of Data from Clinical Studies for Medical Devices
0910-[NEW]
RIN 0910–AG48
PROPOSED RULE 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), the procedures and conditions that FDA[1] is authorized to prescribe for granting an 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 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.

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, 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 the existing regulation, data from clinical studies conducted inside the United States and submitted to support a PMA application may be accepted provided the clinical studies are conducted in compliance with 21 CFR parts 50, 56, and 812. Moreover, data from clinical studies conducted outside the United States and submitted to support a PMA application may be accepted provided the studies are conducted in accordance with ethical principles and the data are valid. Specifically, such clinical studies must either follow the principles of the 1983 version of the Declaration of Helsinki for human subject protection or the laws and regulations of the country where the study is conducted, whichever accords greater protection to human subjects. The use of clinical data varies by type of application or submission, where the use of clinical data is most prevalent for PMA, HDE and IDE applications.

[1] In light of section 903(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" in the discussion of legal authority have been changed to "FDA" or the "agency."

The current regulations do not address FDA's acceptance of clinical data to support 510(k) submissions, and HDE and IDE applications, but in practice, such applications and submissions may be supported by clinical data.
For medical devices undergoing premarket approval review, FDA has always reviewed the safety results of non-IDE clinical trials conducted outside the United States when submitted. Although clinical trials conducted outside the United States are not required to be conducted under an IDE, some sponsors consult with FDA, submit a pre-IDE before initiating a foreign trial, and/or often attempt to develop and implement foreign clinical trials consistent with United States standards for protocol design and good clinical practice. However, with the increased number of multinational studies, some of which may not be under FDA purview, and the increased complexity in a study's protocol, it becomes more difficult to ensure human subject protection and appropriate clinical study conduct.

21 CFR 807.87 – Reporting
Submitters must submit a statement attesting that each study was conducted in compliance with applicable requirements in the protection of human subjects regulations in part 50, the institutional review boards regulations in part 56, and the investigational device exemptions regulations in part 812 of this chapter, or if the study was not conducted in compliance with those regulations, a statement of the reason for the noncompliance. For any clinical studies conducted outside the United States, submitters must submit a statement in accordance with § 812.28(a) and provide supporting information in accordance with § 812.2(e) and § 812.28(b). For any study which was not conducted in accordance with GCP as described in § 812.28(a), the sponsor must include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected.

21 CFR 812.27(b)(4)(i) – Reporting
For clinical studies conducted in the United States, sponsors must submit a statement attesting that each study was conducted in compliance with applicable requirements in the protection of human subjects regulations in part 50, the institutional review boards regulations in part 56, and the investigational device exemptions regulations in part 812 of this chapter, or if the study was not conducted in compliance with those regulations, a statement of the reason for the noncompliance.

21 CFR 812.27(b)(4)(ii) – Reporting
For any clinical studies conducted outside the United States, sponsors must submit a statement in accordance with § 812.28(a), and provide supporting information in accordance with § 812.2(e) and § 812.28(b). For any study that was not conducted in accordance with GCP as described in § 812.28(a), the sponsor must include a statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected.

21 CFR 812.28(a)(1) – Reporting
A statement must be submitted to the FDA by the sponsor or applicant attesting that all such studies have been conducted in accordance with GCP foreign clinical data in order to support an IDE or a device marketing application or submission (an application under section 515 or 520(m) of the act or a premarket notification submission under section 510(k) of the act).

21 CFR 812.28(a)(2) – Reporting
A statement must be submitted to the FDA by the sponsor or applicant attesting to the availability of the data from the study to FDA for validation through an onsite inspection if the agency deems it necessary, and if otherwise authorized by law, or through other appropriate means in order to support an IDE or a device marketing application or submission (an application under section 515 or 520(m) of the act or a premarket notification submission under section 510(k) of the act).

21 CFR 812.28(b) – Reporting
A description of the actions the sponsor or applicant took to ensure that the research conformed to GCP must be submitted to FDA in order to support an IDE or a device marketing application or submission (an application under section 515 or 520(m) of the act or a premarket notification submission under section 510(k) of the act).

21 CFR 814.20 – Reporting
If a clinical study was conducted outside the United States and submitted in support of a PMA, the applicant must submit a statement in accordance with § 812.28(a). For any study that was not conducted in accordance with GCP as described in § 812.28(a), the applicant must submit to the FDA a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected.

21 CFR 814.104 – Reporting
In lieu of the summaries, conclusions, and results from clinical investigations required under §§ 814.20(b)(3)(v)(B), (b)(3)(vi), and the lead paragraph of (b)(6)(ii), the applicant must submit to the FDA any summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefits of the device. To the extent the applicant includes such clinical information, the applicant must include the statements described in §§ 814.20(b)(6)(ii)(A) and (b)(ii)(B) with respect to clinical investigations conducted in the United States and the information described in § 814.20(b)(6)(ii)(C) with respect to clinical investigations conducted outside the United States, where applicable.

21 CFR 812.2(e) – Recordkeeping
For any clinical studies conducted outside the United States to be submitted in support of 1) an IDE, 2) an application under section 515 of the FD&C Act, 3) an application under section 520(m) of the FD&C Act or 4) a premarket notification submission under section

510(k) of the FD&C Act, the sponsor is required to maintain supporting information as described in § 812.28(b) and records retention as described in § 812.28(c).

21 CFR 812.28(c) – Recordkeeping
A sponsor or applicant must retain the records required by this section to demonstrate compliance with the requirements set forth in this section for a clinical study conducted outside the United States if the study is submitted in support of an IDE, for 2 years after the termination or completion of the IDE or if the study is submitted in support of a premarket notification submission, premarket approval application, a notice of completion of a product development protocol, or a humanitarian device exemption application, for 2 years after an agency decision on that submission or application.

21 CFR 812.140- Recordkeeping
An investigator or sponsor must maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, or a premarket notification submission.

2. Purpose and Use of the Information Collection

The proposed rule is intended to update the standards for FDA acceptance of data from clinical studies conducted outside the United States and to help ensure the protection of human subjects and the quality and integrity of data obtained from these studies. As part of this proposed rule, we are also proposing to amend the IDE and 510(k) regulations to address the requirements for FDA acceptance of data from clinical studies conducted inside the United States. The proposed 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 studies should be consistent regardless of the type of submission or application in which the data are submitted to FDA. For data from clinical studies conducted inside the United States, we propose to require statements in 510(k) submissions and IDE applications that are similar to those currently required for PMA applications, to help ensure the protection of human subjects and the quality and integrity of data obtained from these studies. For data from clinical studies conducted outside the United States, FDA believes that revision of the requirements for FDA acceptance of data from these clinical studies is needed for several reasons, such as updating standards for FDA acceptance of data from clinical studies conducted outside of the United States, ensuring quality and integrity of data, standardizing human subject protection, and clarifying requirements for FDA acceptance of data from clinical studies submitted in support of premarket notifications and investigational device exemptions.

The proposed rule would require additional maintenance, retention, and submission of documents indicating (1) clinical studies 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 in this section (and in section #1) allows reviewers to assess the appropriateness and adequacy of the clinical trial design, data collection plans, and protect human subjects participating in medical device trials.

3. Use of Improved Information Technology and Burden Reduction

CDRH is accepting medical device applications in electronic form. The Office of Device Evaluation (ODE) accepts an electronic copy and the Office of In Vitro Diagnostic Device Evaluation and Safety accepts electronic submissions. Both offices are currently developing formal guidelines regarding electronic submissions. Submission of electronic documents rather than paper will be voluntary on the part of manufacturers, and will also meet the requirements of Government Paper Elimination Act (GPEA) Reviewers will have ready access to the electronic submission for reading and review on their desktop computers. Reviewer notes will also be stored electronically directly, without the need to scan paper documents. In the interim, FDA has provided some informal guidance on electronic submissions, entitled "Electronic Copies for Premarket Submissions." Until these electronic submissions are finalized, CDRH/ODE is requesting that industry give prior notification of their desire to submit an application in electronic form. This lead time is important in order to assure that the reviewer has the necessary hardware and software to review the electronic application so that the electronic submission will facilitate the review process.

FDA estimates that 50% of the respondents will use electronic means to fulfill the agency's requirement.

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 studies. 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 small business is estimated to be 99%.

Dunn & Bradstreet (Dunn & Bradstreet, Inc.) data on the number of establishments by employee size for the year 2009 indicate that most of the 17,932 establishments have employee sizes by which they would be considered small. The agency tentatively concludes that the proposed rule would have a significant impact on a substantial number of small entities, but the impact is uncertain.

6. Consequences of Collecting the Information Less Frequently

The information will be collected when a company submits an application for clearance or approval. Because manufacturers determine when a product will be submitted for premarket clearance or approval, the frequency of FDA's receipt of applications (and information collections described in this supporting statement) will be determined by the frequency with which applicants submit applications.

This information collection allows FDA to collect data to ensure that the investigational device's use will not present an unreasonable risk for the subject enrolled in the study 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 Part 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) that each respondent must submit 6 copies of a PMA and 3 copies of a PMA supplement for review. Consequently, information pursuant to this information collection request that is to accompany a PMA will be submitted in multiple copies. FDA maintains the original PMA 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's 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 or PMA supplement is retained for team review by other statisticians, physicians, and scientists.

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

Notice has been published in the Federal Register on February 25, 2013 (78 FR 12664) soliciting comments on this information collection prior to its submission to the Office of Management and Budget (OMB).

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 Parts 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 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), the public information regulations at 21 CFR part 20, and any other applicable regulation governing confidentiality of information or public disclosure of information.

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

21CFR Section	Number of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
807.87	1500	1	1,500	.25 (15 minutes)	375
812.27(b)(4)(i)	400	1	400	1	400
812.27(b)(4)(ii)	100	1	100	.25 (15 minutes)	25
812.28(a)(1)	1500	1	1,500	.25 (15 minutes)	375
812.28(a)(2)	1500	1	1,500	.25 (15 minutes)	375
812.28(b)	1500	1	1,500	10	15,000
814.20	10	1	10	.50 (30 minutes)	5
814.104	10	1	10	8	80
Total Burden Hours					16,635

Table 2. – Estimated Annual Recordkeeping Burden (Ongoing)

21CFR Section	Number of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
812.2(e)	500	1	500	1	500
812.28(c)	1500	1	1,500	1	1,500
812.140	10	1	10	1	10
Total Burden Hours					2,010

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 18,645 annual hours. FDA based the estimated number of respondents on the most recent empirical data for 510(k), PMA, HDE, PDP, and IDE submissions received by FDA. Time estimates for statements attesting each study was performed 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 annual reporting and recordkeeping cost to respondents for submitting and maintaining information relating to human subject clinical trials is $979,245. This figure was derived by multiplying the total reporting burden hours from Table 1 by an hourly rate of $55. This hourly rate is based on 2,080 annual work hours and an annual salary rate of $116,000. This health care professional salary rate includes salary, benefits, overhead, technical staff, support staff, etc. and was determined by the agency's current estimates of staff expenses.

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Healthcare professionals	16,635	$55	$914,925
Recordkeepers	2010	$32	$64,320
Total			$979,245

Using FY10 data, FDA estimates that recordkeeping (Table 2 above) costs for respondents is $64,320. This figure was determined by multiplying the total number of hours estimated for recordkeeping (2010) by $32.00. Historical submissions, trend analysis, and estimates for annual cost of living increases determined the hourly rate.

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

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	6,520	0.25	$51	$83,130

The estimated time for review and data entry is 15 minutes, yielding a total of 1630 hours for reviewing all responses. The information will be extracted by program personnel at a GS-14 salary cost of $51 per hour for a total cost to the Federal Government of $83,130.

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.