

U.S. Food and Drug Administration

SUPPORTING STATEMENT FOR

Investigational Device Exemptions; Modifications

21 CFR Part 812

OMB No. 0910-0391

SECTION A - Justification

1. Circumstances Necessitating Information Collection

The Food and Drug Administration (FDA) is requesting approval of information collection requirements in 21 CFR Part 812 set forth in the attached final rule (Attachment A).

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j(g)) (Attachment B) authorizes FDA to establish procedures under which devices may, upon application, be granted an exemption from certain provisions of the Act including the requirement to obtain FDA premarket clearance of a device, to permit the investigational use of such devices by experts qualified by scientific training and experience to investigate the safety and effectiveness of the device.

On November 21, 1997, the President signed into law the Food and Drug Modernization Act (FDAMA). Section 201 of FDAMA amended the act by adding new section 520(g)(6) (21 U.S.C. 360j(g)(6)). Section 520(g)(6) of the act permits, upon promulgation of a regulation, certain changes to be made to either the investigational device or the clinical protocol without prior FDA approval of an IDE supplement. Specifically, this section of the statute permits:

"(i) developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in the basic principles of operation and that are made in response to information gathered during the course of an investigation; and

(ii) changes or modifications to clinical protocols that do not affect --

I) the validity of the data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol;

(II) the scientific soundness of an investigational plan submitted [to obtain an IDE]; or

(III) the rights, safety, or welfare of the human subjects involved in the investigation."

The new law specifies that the implementing rule provide that such changes or modifications may be made without prior FDA approval if the IDE sponsor determines, on the basis of credible information (as defined by the Secretary), that the above conditions are met; and if the sponsor submits, not later than five days after making the change or modification, a notice of the change or modification.

Because both the current IDE regulation and the new statute permit certain changes to be made to the investigational plan without prior agency approval, FDA views section 520(g)(6) of the act as consistent with the way the agency has previously interpreted 21 CFR 812.35(a). Nevertheless, in order to track the new statutory language more closely, FDA is amending 21 CFR 812.35(a) to permit changes to the investigational device, including manufacturing changes, or to the clinical protocol, in accordance with the criteria identified in section 520(g)(6) of the act. This rule defines the credible information to be used by sponsors to determine if the statutory criteria are met. Finally, the amended regulation provides clarification regarding the types of changes that could be made to other parts of the investigational plan (i.e., other than changes to the device or clinical protocol) without prior agency approval and be reported in the annual progress report.

FDA is requesting OMB approval for the following new information collection requirement established by the rule on modifications to investigational devices and investigational device protocols.

812.35(a)(3)(C) - Notice of IDE Modification

A sponsor may make changes to an investigational device or to a protocol, if the sponsor determines that the changes meet the criteria described in the regulation and if the sponsor submits a notice to FDA within 5 days of making the change.

For a developmental or manufacturing change to the device, the notice shall include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice shall include a summary of the information which served as the credible information supporting the change.

For a protocol change, the notice shall include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information which served as the credible information supporting the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects.

2. By Whom, and for What Purpose the Information is to be Used

The information will be used by FDA to determine whether the changes may have a significant effect on the safety or effectiveness of the device and, therefore, whether FDA needs additional information to determine whether other action is necessary to protect the public health.

3. Consideration of Information Technology

In the **Federal Register** of March 20, 1997, FDA issued a final regulation (21 CFR Part 11) (Tab C) that would, under certain circumstances, permit the agency to accept electronic signatures and handwritten signatures executed to electronic records as generally equivalent to paper records and

handwritten signatures executed on paper. These regulations would apply to records, when submitted in electronic form, that are required in Title 21 of the Code of Federal Regulations (CFR) such as IDE modifications. The use of electronic forms of record keeping and reporting submissions to FDA remains voluntary. The intended effect of this regulation is to permit use of electronic technologies in a manner that is consistent with FDA's overall mission and that preserves the integrity of the agency's enforcement activities.

4. **Efforts to Identify Duplication and Similar Information Already Available**

The required information concerning modifications of investigational devices and protocols is only available from the sponsor of the investigation.

5. **Small Businesses**

The information collection will not have a significant economic impact on a substantial number of small entities. The rule would simplify the way in which modifications are made and reported to FDA.

6. **Consequences of Less Frequent Information Collection and Technical or Legal Obstacles**

Applications are required within 5 working days of making the change in accordance with the law as amended by FDAMA. This reporting is necessary to assure that changes that may affect the public health are identified and dealt with quickly.

7. **Consistency with the Guidelines in 5 CFR 1320.5(d)(2)**

The collection is entirely consistent with 5 CFR 1320.

8. **Consultation Outside the Agency**

In the **Federal Register** of July 15, 1998, FDA submitted the information collection requirements in the proposed rule to the Office of Management and Budget (OMB) for review, and invited interested persons to submit comments on the information collection requirements to OMB. Most comments discussed directly or indirectly impact the information collection requirements. FDA has responded to these comments in detail in Section II of the attached final rule.

Several comments stated that 5 day notices should be submitted only for changes that had been submitted previously in IDE supplements. These comments stated that the requirement of 5 day notices was more burdensome if it was required for changes that had been submitted previously as annual reports.

FDA believes that the language in section 520(g)(6) of the act clearly requires that certain changes that previously were submitted as annual reports now be submitted as 5 day notices. Nonetheless, FDA believes that the final regulation will reduce burden on industry in two ways. First, section 520(g) codifies and therefore makes mandatory, FDA's previous practice of allowing certain changes to be implemented by notification to FDA in an annual report. Second, this regulation provides clarification on the types of changes that could be implemented without prior agency approval, thus eliminating the submission of unneeded IDE supplements.

Finally, FDA believes that the submission of a 5 day report for certain changes that previously were submitted in annual reports will not impose any appreciable additional burden on industry because both the evidence used to determine whether a change may be made under an annual report and a 5 day notice provision is the same, and would need to be generated and evaluated before the change is implemented. Accordingly, a requirement to send information that is available before the change is made within 5 days of the change, as opposed to a later time after the change, is not an appreciable additional burden.

Several comments stated that the proposed definitions of credible information necessary to support a 5 day notice were unduly burdensome. For design changes, the proposed rule stated that credible information would consist of information generated by design controls. For protocol changes, the proposed rule stated that credible information would consist of approval of an IRB, concurrence of a DSMB, or peer reviewed literature.

Many comments objected to the concurrence of IRB's and DSMB's as credible information because they stated that third party review for changes that previously had not required such review was burdensome. Some of the reasons specifically stated that FDA had not adequately considered the costs to sponsors to obtain this type of review.

In response to these comments, the final rule has eliminated the requirement for IRB approval or DSMB concurrence as evidence of credible information, and instead requires documentation such as peer reviewed published literature, the recommendation of clinical investigator(s), and/or a summary of the data gathered during the clinical trial that supports the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects. At the time a sponsor changes a device protocol, this type of evidence is already generated and evaluated. Therefore, FDA's definition of credible information in the final rule provides flexibility and negligible additional burden in that it requires the submission of already existing evidence.

Other comments objected to the lack of flexibility in the requirement for credible evidence for design changes., These comments supported the proposal to use information generated by design controls, but stated that FDA should also allow other information. FDA has addressed these concerns in the final rule by allowing other information to be used as a basis for credible information to support a design change.

Some comments requested that FDA allow more time for the submission of reports by allowing reports to be made within 5 working days of the change instead of 5 calendar days. FDA has stated in the preamble to this final rule that 5 working days from the change is the appropriate time frame for submissions. This policy should allow sponsors to reduce costs by allowing them additional time to prepare notices.

One comment suggested that the requirements for the contents of a 5 day notice were unduly burdensome in that the statute required a notice and not a detailed description of the changes. The comment further suggested that FDA should require only a notice of the change while the detailed description would be reported in the annual report.

FDA does not agree with this comment. As modified in the final rule, the information submitted to the agency in the 5 day notice is the same information that the sponsor would have submitted in the annual report, and therefore, should not represent an increased burden. Moreover, the submission of less information would not allow FDA to notify sponsors that changes require a full supplement

until the time of the annual report, and therefore may result in sponsors wasting resources gathering data that ultimately may not be used.

9. **Payments or Gifts to Respondents**

FDA will not provide any payments or gifts to sponsors of modified IDE's.

10. **Confidentiality of Information**

Information in treatment use IDE's will only be released in accordance with FDA regulations implementing the Freedom of Information Act, 21 FR Part 20 (Attachment D). Patient information as well as confidential commercial information will be protected from disclosure.

11. **Sensitive Questions**

The information collection does not include questions concerning sex, behavior, attitudes, religious beliefs, or private matters.

12. **Estimates of Burden Hours and Explanation**

Table 1 provides an estimate of the annual reporting burden for sponsors of IDE's that are modified. An explanation of the hour burden estimate follows the table and an explanation of the total cost estimate is provided in item 13 below.

Table 1 - Estimated Annual Reporting Burden for Sponsors of IDE Modifications

CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
812.35(a)(3) (C)	300	1	300	10	3,000

There are no capital costs or operating and maintenance costs associated with this collection of information.

Explanation of Reporting Burden Estimate

Based on its experience with reviewing investigational device exemptions, FDA estimates that 300 Notices of IDE Modification will be submitted each year. Based upon FDA's knowledge of the preparation of IDE's FDA estimates that it will take approximately 10 hours to prepare a Notice of IDE Modification. Thus, the total annual burden for preparing notices will be 3,000 hours (300 notices x 10 hours per notice).

Estimate of Annualized Cost to Respondents for the Hour Burdens

FDA estimates that the average hourly cost (including overhead) for preparing Notices of IDE Modification will be \$40. This will result in a total annual cost of \$120,000 (3,000 total hours x \$40).

13. Annual Cost to Respondents

There will be no cost to respondents above the reporting hour burden set out in section 12 above.

14. Annual Cost to Government

FDA estimates that it will use approximately one full-time equivalent per year to review the applications and quarterly reports. This will result in an annual cost to the government of approximately \$89,700 for this FTE & overhead.

15. Changes in Burden

This is a new information collection which accounts for the program change reported in item 13 of OMB Form 83-I.

16. Statistical Reporting

FDA does not intend to publish the results of this information collection.

17. Exemption for Display of Effective Date

FDA is not seeking an exemption for display of the effective date.

18. Exception to the Certification Statement

There are no exceptions to the certification statement identified in item 19 of OMB Form 83-I.

SECTION B - Collection of Information Employing Statistical Methods

The collection of data does not employ statistical methods.

[Information Collection Requests](#)**[GUIDELINES TO OBTAIN OMB APPROVAL FOR COLLECTIONS OF INFORMATION REQUIREMENTS](#)**