

OMB INFORMATION COLLECTION
Financial Disclosure by Clinical Investigators - 21 CFR 54
SUPPORTING STATEMENT

JUSTIFICATION

1. Circumstances Necessitating Information Collection

The Food and Drug Administration is requesting OMB approval of the information collection requirements contained in 21 CFR 54.4 that are listed below. (See Attachment A).

21 CFR 54.4 - Reporting by Clinical Investigators

Clinical Investigators subject to IND or IDE regulations must provide the sponsor of the study with sufficient accurate information needed to allow subsequent disclosure or certification.

21 CFR 54.4(1) - Reporting by Sponsors of Product Marketing Applications

The sponsor of an application submitted under sections 5.5, 506, 507, 510(k), 513, or 515 of the Federal Food Drug, and Cosmetic Act, or section 351 of the Public Health Service Act, that relies in part on clinical studies shall submit for each clinical investigator who participated in a covered clinical study either a certification as described in paragraph (a) (1) of this section, or a disclosure statement as described in paragraph (1) (3) of this section.

21 CFR 54.6 - Recordkeeping

A sponsor who has submitted a marketing application containing covered clinical studies shall keep on file certain information pertaining to the financial interests of clinical investigators.

FDA has become increasingly aware of the existence of potentially problematic compensation arrangements between sponsors of FDA-regulated products and clinical investigators who conduct clinical studies of the sponsors' products to determine whether they meet FDA marketing requirements. Examples include payment schemes whereby the value of the compensation to the clinical investigator in the form of generous grants to fund ongoing research, expensive laboratory equipment, retainers for ongoing consultation, and honoraria. The agency is also aware of proprietary and equity interests of some clinical investigators in the tested products, or in the sponsors of these products. Among the sources of the agency's information are published newspaper articles, congressional reports, a Government Accounting Office report, congressional inquiries, and public testimony and comments.

These arrangements clearly have the potential to bias the results of clinical studies that are critically important in establishing the safety and effectiveness of products that can impact on public health and well being. However, up to now, FDA has had no formal mechanism to learn

of the existence of such arrangements and to obtain information on them--a situation identified by the Inspector General of the Department of Health and Human Services in a 1991 management advisory report as a potential material weakness under the Federal Managers' Financial Integrity Act. FDA has concluded that there is a need for the agency to collect this information in order to strengthen its product reviewing process, to help assure safe and effective therapeutic products for public use, and to clarify for sponsors and investigators the arrangements the agency finds problematic. Clinical studies can be designed to minimize the occurrence of bias from arrangements that FDA has identified, and the agency affirms that it will work with sponsors on the design of studies to help preclude questions on data integrity from arising in the course of product review.

2. How, By Whom, Purpose of Collection

The information to be collected from sponsors of product marketing applications will be submitted to FDA as part of the marketing applications, using forms prepared by FDA and submitted to OMB for approval. For each clinical investigator who took part in a covered clinical study, the sponsor will either certify that the investigator has no financial interest or arrangement identified in §54.4 (a)(3), or will disclose identified interests and arrangements held by the clinical investigator and describe steps taken to minimize potential bias of such interests and arrangements on the clinical study results. Clinical investigators will provide sponsors with sufficient accurate information to enable the sponsor to submit certification and disclosure statements. Certification of a clinical investigator will help to assure FDA reviewers of the integrity of a clinical study. Disclosure of an identified interest or arrangement and steps taken to minimize potential bias will be used by reviewers to evaluate whether the integrity of the study may be relied on. When identified interests or arrangements are disclosed, FDA will respond in one of the following ways: If the clinical study in which the investigator participated was well designed and managed, FDA may accept the data without further question. If a clinical investigator's financial interests and arrangements raise serious questions about the integrity of the data, and the study design does not include sufficient bias-minimizing steps to offset these questions, FDA can initiate audits of the data by reviewers, request further analyses of the data from the sponsor, request that the sponsor conduct additional studies to confirm the potentially biased study, or refuse to treat data from the study as pivotal or primary data upon which an agency action could be taken. Under currently applicable product review regulations, reviewers can and do request further analyses of data from a sponsor as appropriate, or request that a sponsor conduct additional studies to confirm the results of a questionable study.

3. Consideration Given to Information Technology

In a separate rulemaking, FDA established procedures for acceptance of electronic records and signatures. Sponsors may electronically maintain and make available records in accordance with the requirements in §54.6. FDA will also accept electronic submissions, such as required under §54.5(a) to the extent allowed by the agency's capability for automated data processing of marketing applications. FDA is working to improve this capability, with the goal of eventually accepting electronically all submissions related to product review.

4. Identification of Information

In drafting this regulation, FDA consulted with the Public Health Service (PHS) and National Science Foundation (NSF), which have issued respectively a final rule and a policy statement on financial disclosure by scientific investigators. It needs to be noted that the PHS and NSF documents respond to principles that govern federally funded grants and contracts. Such funds are granted for all types of research, and these organizations must guard against bias in all types of research. In contrast, FDA must rely on clinical data in making safety and effectiveness determinations for regulated products, and FDA's primary interest is in clinical data. There is potential for the FDA and PHS regulations to overlap in a very small number of instances involving PHS-funded clinical research on FDA-regulated products. In the preamble to the proposed regulation, FDA asked for public comment on whether, in such instances, meeting the PHS requirement for disclosure should be considered to meet FDA's requirement.

Based on comments received and further deliberation, FDA has concluded that FDA's reporting requirements meet different needs for the most part and the information submitted in the PHS and NSF formats does not overlap and is not adequate for product review purposes.

As there is currently no FDA mechanism for requiring the information that would be submitted under the FDA proposed rule, there is no internal duplication. There is no similar information available to FDA.

5. Small Businesses

FDA has conducted a Regulatory Flexibility Analysis of this regulation and concludes that it will not have a significant impact on a substantial number of small businesses. This is the case because in developing the regulation FDA has kept in mind that, not only are the majority of firms that submit marketing applications to FDA of a size to be considered small businesses by the Small Business Administration, but also the firms most apt to be affected by the disclosure provisions of this regulation are small entities of two types: (1) firms whose owners are likely to have developed the tested product and who serve as clinical investigators, and (2) small start-up firms that are not heavily capitalized and provide clinical investigators with equity interests as reimbursement. FDA has addressed the need to minimize burden in a number of ways. The final rule will not prohibit any financial interest, such as compensation to investigators in the form of equity in the sponsor's firm, nor is the agency proposing to require divestiture by the investigator of any financial interest, because such provisions could impact significantly on small entities and hinder their ability to bring innovative products to market. The reporting and recordkeeping burdens are the minimum necessary to achieve the goals of the proposed regulation.

Submission of the required information has been made as simple as possible for small entities.

FDA has developed forms for certification and disclosure and for certification, and a sponsor may submit one form for all clinical investigators for whom certification is being made.

The required information is to be submitted as part of a product marketing application, which

amounts to a one-time collection. The concept of less frequent collection is not applicable.

6. Less Frequent Information Collection

Without the information that is required by this regulation, FDA lacks the means to evaluate whether clinical data submitted in support of the safety and effectiveness of a regulated product are vulnerable to a recognized source of potential bias, and to assure that the public health is not threatened with the consequences of biased data.

7. Information Collection Circumstances

There is one special circumstance to explain: The records required to be kept under §54.6 of this regulation would be retained by sponsors for 2 years after the date of approval of the application. As such records will be generated at the outset of a clinical trial, it is conceivable that they would be kept by sponsors for more than 3 years. Two years after the date of approval of the application is the normal period of time for retention of all other information related to an application.

8. Consultations with Persons Outside FDA

In the February 2, 1998, final rule (63 FR 5233- 5249), FDA requested comments on the information collection provisions of the final rule. The agency received three comments in response to this request.

One of the comments was very similar to the petition for reconsideration to which this revised final rule responds. Another comment suggested that FDA use different criteria for disclosure of equity interests depending on the amount of sponsor capital. FDA disagrees. The \$50,000 threshold was chosen to represent a dollar amount that could be important to an investigator. During the rulemaking, many comments were received on the issue of the appropriate threshold. Some suggested that FDA's rule should be made consistent with the Public Health Service final rule and the National Science Foundation statement of policy on Objectivity in Research published on July 11, 1995 (a considerably more stringent requirement than the disclosure requirement in FDA's final rule); others suggested different dollar thresholds, such as \$10,000, or particular percentages of company equity. One comment suggested that investigators be banned from owning an equity interest in a sponsor that exceeded \$25,000 a year. FDA's original proposal of a percent equity threshold was deleted from the final rule because the agency recognized that for many corporations this would represent an unrealistically large interest (e.g., 5 percent of a \$10 million company is \$500,000). Based on discussions with FDA's Science Board and comments received on FDA's proposed rule, FDA continues to believe that a \$50,000 disclosure threshold strikes the appropriate balance between the agency's need to be aware of, and to help minimize, the potential for bias in clinical data. This comment also stated that FDA underestimated the amount of time necessary to collect, analyze, and store the information needed to comply with the February 2, 1998, final rule. FDA agrees that the

time estimates in that document may have been too low because FDA was not able to accurately predict the burden associated with collecting information from past covered clinical trials. FDA continues to believe that the majority of applicants will certify to the absence of covered financial interests and that sponsors will incorporate the collection of this information into the routine administration of their studies. FDA agrees that additional time would have been needed to gather information from investigators in past studies prior to the revisions made by this final rule. As FDA is revising the rule to eliminate most retrospective reporting, however, the burden will be significantly less than it would have been under the February 2, 1998, final rule. The agency has reevaluated its burden estimate and concludes that, although the estimate in the February 2, 1998, final rule (63 FR 5233 at 5249) underestimated the burden of retrospective reporting at that time, it now accurately reflects the lessened burden of the financial disclosure regulations as revised by this final rule. Therefore, the agency is not modifying its burden estimate. Finally, a comment requests guidance from FDA on what the comment characterizes as ambiguities in the final rule. FDA has provided clarification through revisions made to this final rule. FDA declines to issue a guidance document before the rule becomes effective; however, FDA will assess the need for guidance after the agency and those subject to the rule have gained some experience with its implementation. A second comment suggested that FDA modify section 9 of Form FDA 1572, "Statement of Investigator," to add a commitment that the investigator will comply with the financial disclosure regulations and to state whether the investigator holds a significant equity interest in the sponsor. The comment stated that this change to Form FDA 1572 would eliminate the need for investigators to complete additional documentation. FDA does not agree with the comments' recommendation that Form FDA 1572 be changed. Clinical investigators are already required to comply with the financial disclosure regulations and, as part of this obligation, must provide financial information to the sponsor under 21 CFR 312.53(c)(4) and 312.64(d) of the final rule. The agency has developed FDA Forms 3454 and 3455 in an effort to facilitate the collection of this information. FDA also notes that the proposed change would not eliminate the need for the investigator to provide the details of any significant equity interests as required by the final rule. Therefore, the recommended change would make Form FDA 1572 more burdensome without reducing the burden under the final rule. A third comment submitted by two clinical investigators from a government agency asked that a division within a Federal Government agency be exempted from reporting financial interests to FDA because it does not submit marketing applications to FDA for products tested under its investigational new drug application (IND's) and because, according to the comment, its phase III studies are designed, monitored, and assessed in such a way that the studies are not subject to the same potential bias found in smaller, investigator-initiated or company-sponsored studies. A government researcher conducting a clinical study under an IND held by a government agency does not have to report financial interests or arrangements to FDA, as it is the submission of a marketing application that triggers the disclosure requirement. If, however, the study were used to support an application, the applicant would be required to report any covered financial interests of the clinical investigators. FDA declines to make a change in response to this comment.

9. Payment or Gift

Not applicable.

10. Confidentiality Provisions

FDA has made no guarantees of confidentiality to sponsors and clinical investigators, but in almost all cases will treat this information as confidential. Information such as a proprietary interest in the tested product is already public information and, therefore, releasable. Otherwise, FDA will consider disclosed information as confidential and will consider release of such information only in circumstances in which questions of propriety clearly outweigh the privacy interest. FDA believes that such cases will involve only a small subset of those clinical investigators.

11. Privacy

Not applicable.

12. Burden of Information Collection

These sponsors represent pharmaceutical, biologic, and medical device firms. Many of these firms are small entities, especially those which manufacture medical devices and biotechnology products. Respondents are also clinical investigators who provide financial information to the sponsors of marketing applications. The applicant will incur reporting costs in order to comply with the final rule. Applicants will be required to submit, for example, a complete list of clinical investigators for each covered study, a list that is already submitted in a marketing application. For investigators not employed by the applicant and/or the sponsor of the covered study, the applicant must either certify to the absence of certain financial arrangements with clinical investigators or disclose those arrangements to FDA. FDA expects that almost all applicants will submit a certification statement under 21 CFR 54.4(a)(1) and (a)(2). Preparation of the statement using the following Form FDA 3454 will represent little effort and should require no more than 1 hour per study.

Table 1. -- Estimated Number of Applications, Clinical Trials, and Investigators Subject to the Proposed Rule by Type of Application ¹

Application Type	Total Number of Applications	Number of Applications Affected	Number of Trials	Number of Investigators
Drugs: •New drug application (NDA), new molecular entity (NME)	35	35	3 to 10	3 to 100

•NDA nonNME	100	100	1 to 3	10 to 30
NDA efficacy supplement	100	100	1 to 3	10 to 30
Abbreviated new drug application (ANDAs)	400	240	1.1	2
ANDAs supplement	2500	120	1	2
Rx switch	20	10	2	4
Biologics:				
•Product license application (PLA)	25	25	3 to 10	3 to 100
•PLA efficacy supplement	10	10	1 to 3	3 to 100
Medical Devices:				
•Premarket approval (PMA)	50	50	1	10 to 20
•PMA supplement	40	10	1	3 to 10
•Reclassification devices	8	4	1	3 to 10
•510(k)	6000	300	1	20

¹ Source: Agency estimates

When certification is not possible and disclosure is made using form FDA 3455, the applicant must describe the financial arrangements or interests and the steps that were taken to minimize the potential for bias in the affected study. As the applicant will be fully aware of those arrangements and the steps taken to address them, describing them will be straightforward. The agency estimates that it will take about 4 hours to prepare this narrative.

Until the agency begins to collect information on the financial arrangements between investigators and applicants, it cannot know the actual number of disclosable arrangements. Therefore, it is not possible to predict the total cost to industry of preparing these explanatory statements with any certainty because the financial arrangements described in this rule are uncommon. FDA estimates that from 1 to 10 percent of the applications would need disclosure statements, and has used the extremely conservative estimate of 10 percent in Table 2 or this document.

Investigators must provide sponsors of the covered studies with sufficient accurate information to make the required disclosure or certification. Because much of the information required can be obtained from the applicant's own records, the costs incurred by the clinical investigator will be minimal. Clinical investigators are required to do one of two things: (1) Provide a statement that they, their spouse, and their dependent children did not have a significant equity interest as defined in 54.2(b) in the sponsor of the covered study, or (2) disclose any such interest. Clinical investigators are accustomed to supplying such information in even greater detail when applying for research grants. Most people know the financial holdings of their immediate family, and records of such interests are generally accessible because they are needed for preparing tax records. FDA estimates that the time required for this task may range from 5 to 15 minutes.

Table 2. -- Estimated Annual Reporting Burden ¹

21 CFR Section	No. Of Respondents	No. Of Respondents per Respondent	Total Annual Responses	Hours per Response	Total Hours
54.4(a)(1) and (a)(2)	1,000	1	1	1	1,000
54.4(a)(3)	100	1	1	4	400
54.4 (Clinical Investigators)	46,000	1	1	.10	4,600
Total					6,000

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Certification: FDA received an average of 1000 marketing applications each year that contain clinical data. The agency estimates that virtually all of the 1000 sponsors submitting marketing applications will be able to certify for one or more investigators, and the names of all investigators for whom the sponsor is certifying may be attached to one certification form. The agency estimates that preparation of the certification form will take at most 1 hour, of which 80% will be clerical time (\$10.48/hr.) and 20% management time (\$15.23/hr.) plus 30% for overhead, providing a weighted wage rate of \$11.86/hr. The agency bases this estimate on sampling of time taken in preparation of other portions of marketing applications. The total estimated time spent by sponsors of marketing applications on certification in a given year is estimated to be 1000 hours.

Disclosure: FDA has no firm basis for estimating the frequency of disclosure, but believes that at most 10% of sponsors submitting marketing applications, i.e., 100 sponsors, will be required to disclose financial interests and arrangements for one clinical investigator. The agency estimates that preparation of the disclosure form, which includes identifying the interest or arrangement held by the investigator and describing steps taken to minimize bias of study results, will take 4 hours, of which 90% will be management time (\$15.23/hr.) and 10% clerical time (\$10.48/hr.) plus 30% overhead, providing a weighted wage rate of \$19.18/hr. The total estimated time spent by sponsors of marketing applications on disclosure in a given year is estimated to be 400 hours.

Recordkeeping: As stated, recordkeeping will require minimal time because a sponsor will be able to incorporate financial disclosure information into the sponsor's existing system for maintaining investigator information. It is estimated that an average of 15 minutes will be needed for inclusion of this information in an application record. In calculating the cost of recordkeeping, the same weighted wage rate is used as for certification: \$11.86/hr.

Sponsors must also submit a complete list of clinical investigators for each covered study; however, this list is already a requirement for a marketing application and thus no new costs will be incurred for this information.

Clinical investigators must report to sponsors, in whose studies they participate, sufficient,

accurate information to enable the sponsor to complete certification and disclosure forms. Most clinical investigators will have no disclosable information to report to the sponsor, and for these investigators reporting will amount to checking a box or writing the equivalent of “no disclosable financial arrangements.” Even if an investigator holds disclosable interests or arrangements, most of this information will already be known by the sponsor: i.e., a financial arrangement between the sponsor and the clinical investigator whereby the value of the compensation to the investigator could be influenced by the outcome of the study; any significant payments of other sorts to the clinical investigator by the sponsor; any proprietary interest in the tested product held by the clinical investigator; and, if the sponsor is not a publicly held corporation, any significant equity interest in the sponsor that is held by the investigator. The investigator will need only to provide the sponsor with information concerning a significant equity interest in the sponsor, providing the sponsor is publicly held. Because the investigator will have such information readily available for tax purposes, FDA estimates that only minimal time will be spent by the investigator in providing this information to the sponsor. FDA believes the average time spent by a clinical investigator in providing a sponsor with the required financial information will be .10 hours. Some 46,000 clinical investigators participate in covered clinical studies in a given year. Thus, a total of 4,600 burden hours is estimated for reporting by clinical investigators to sponsors in a given year. Cost of this burden is figured using a physician's mean hourly wage of \$87.69.

The following costs are projected for reporting and recordkeeping activities associated with this regulation:

Sponsors' costs:

Certification:	1,000 hours @ \$11./86/hr.	\$11,860
Disclosure:	400 hours @ \$19.18/hr.	7,672
Recordkeeping:	250 hours @ \$11.86/hr.	+ <u>2,965</u>

Sponsors' total costs \$22,497

Clinical Investigators' costs:

Reporting:	4,600 hours @ \$87.69/hr.	\$403,374
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Total costs to sponsors and investigators \$425,871

13. Costs to Respondents

There are no additional information collection costs to respondents and recordkeepers beyond those estimated in the previous item. This is because the information will be collected and submitted as part of preparation of a marketing application, and sponsors already have in place processes and equipment for collecting and maintaining information from clinical investigators who study FDA-regulated products. Investigators who participate in clinical studies of regulated products are required to provide sponsors of the studies with a variety of information and are thus accustomed to this activity.

14. Costs to Federal Government

Because FDA already has in place equipment and processes for handling information contained in product marketing applications, the information collected under this regulation will generate new costs to the agency in only two areas:

- (1) Additional review of applications to assure that the required information has been submitted, and all clinical investigators participating in covered studies are accounted for. Agency staff estimate that this review could take from 15 to 20 minutes for an application in which all clinical investigators are certified to upwards of 5 hours for an application which includes disclosure for an investigator. For planning purposes, an average of 2 hours has been assigned to this review. The initial review and assessment of applications would be conducted by a consumer safety officer at an average hourly rate of \$28.88 (average hourly wage rate of consumer safety officers in the Center for Biologics Evaluation and Review, the Center for Devices and Radiological health, and the Center for Drug Evaluation and Review).
- (2) An agency data audit of a covered clinical study. If a clinical investigator's financial interests and arrangements raise serious questions about the integrity of the data, and the study design does not include sufficient bias-minimizing steps to offset these questions, one course of action FDA can take is to request a data audit by agency bioresearch monitoring staff. Without previous experience, it is difficult to estimate the frequency with which data sites would not otherwise be inspected. FDA estimates that 10% of sponsors of marketing applications will submit disclosures for clinical investigators in a given year. The agency estimates that only a very few would be sufficiently serious, and study design sufficiently questionable, to trigger a data audit. For planning purposes, the agency has set this figure at one-half of one percent of submitted applications, or 5 applications. A data audit may cover a wide range of time, based on the size and complexity of a study and the number of investigators participating, but 40 hours is a realistic average time for such an audit. The cost per hour is the agency's average hourly wage rate of \$28.88 for a consumer safety officer who would conduct the review.

Estimated Annual costs to FDA:

Additional Review:	2 hrs. @ \$28.88 for 1,000 applications	\$57,760.00
Data Audit:	40 hrs. @ \$28.88 for applications	<u>5,776.00</u>
Total		\$63,536.00

15. Reason for Change

FDA has not previously collected the information covered by this final regulation.

16. Statistical Reporting

Results of this information collection will not be published.

17. Display of OMB Approval Date

FDA is not seeking approval to not display the expiration date for OMB approval of the information collection.

18. Exceptions to "Certification for Paperwork Reduction Act Submissions"

There are no exceptions to the certification statement in item 19, "Certification for Paperwork Reduction Act Submissions," of OMB Form 83-I.