Financial Disclosure by Clinical Investigators - 21 CFR 54
SUPPORTING STATEMENT
2009

JUSTIFICATION

1. Circumstances making the Collection of Information Collection Necessary

The Food and Drug Administration, FDA is requesting approval the information collection requiring the sponsors of any drug, biologic, or device marketing application to certify to the absence of clinical investigators and/or disclose those financial interests as required, when covered clinical studies are submitted to FDA in support of product marketing.

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.

The applicant covered by this section shall submit for all clinical investigators (as defined in §54.2(d)), to whom the certification applies a completed Form FDA 3454 attesting to the absence of financial interest and arrangements described in paragraph (a)(3) of this section.

For any clinical investigator defined in §54.2(d) for whom the applicant does not submit the certification described in paragraph (a)(1) of this section, the applicant shall submit a completed Form FDA 3455 disclosing completely and accurately the following: any financial arrangements, any significant payments , any proprietary interest, any significant equity interest, and any steps taken to minimize the potential for a bias resulting form any of the disclosed arrangement, interest, or payments.

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 agencys 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. Purpose and Use of Information 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 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 is used by reviewers to evaluate whether the integrity of the study may be relied on. When identified interests or arrangements are disclosed, FDA responds 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 investigators 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 initiates 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 can 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. Use of Improved Information Technology and Burden Reduction

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 agencys 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. Efforts to Identify Duplication and Use of Similar Information

In drafting this regulation, FDA consulted with the Public Health Service (PHS) and National Science Foundation (NSF), which have issued respectively a regulation 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 FDAs 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 FDAs requirement. Based on comments received and further deliberation, FDA has concluded that FDAs 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 regulation, there is no internal duplication. There is no similar information available to FDA.

5. Impact of Small Businesses or Other Small Entities

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 regulation will not prohibit any financial interest, such as compensation to investigators in the form of equity in the sponsors 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 no applicable.

6. Consequences of Collecting the Information Less Frequently

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. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

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

In the Federal Register of December 29, 2008 (73 FR 79493), FDA published a 60-day notice requesting public comment on the information collection provisions. Two comments were received, one comment expressed support for this information collection. The second comment raised several issues, first, the issue of the current cost the commenter incurs in the collection of Financial Disclosure and the estimate of substantial operating costs the commenter incurs in operating costs to support the collection of investigator financial information. FDA appreciates the comment and based on this new data, submitted by the commenter, will undertake a new evaluation whether there are capital costs or operating and maintenance costs associated

with this collection of information. FDA also appreciates the comment concerning the definition of ``clinical investigator'' and will forward the comment to the FDA office responsible for this collection of information to consider in any future rulemaking. However, these definitions are codified in 21 CFR 54.2. FDA also appreciates the comment regarding the use of Form FDA 1572 to minimize burden. However, 21 CFR 54.4 requires the use of Form FDA 3454 and Form FDA 3455. This comment will also be forwarded to the FDA office responsible for this collection of information to consider in any future rulemaking.

9. Explanation of Any Payment or Gift to Respondents

Not applicable**.**

10. Assurance of Confidentially Provided to Respondents

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. Justification for Sensitive Questions

Not applicable.

12. Estimates of Annualized Burden Hours and Costs

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 regulation. 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 Regulation by Type of Application [1]

Application Type	Total Number of Applications	Number of Applications Affected	Number of Trials	Number of Investigations
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 (ANDA)	400	240	1.1	2
ANDA 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.

FDA estimates that 25 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	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
54.4(a)(1) and (a)(2)form 3454	1,000	1	1,000	5	5,000
54.4(a)(3) form 3455	100	1	100	20	2,000
54.4 (Clinical Investigators)	46,000	.25	11,500	.1	11,500
Total					18,500

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

The sponsors of covered studies will be required to maintain complete records of compensation agreements with any compensation paid to nonemployee cli8nical investigators, including information showing any financial interests held by the clinical investigator, for a time period of 2 years after the date of approval of the applications. This time is consistent with the current recordkeeping requirements for other information related to marketing applications for human drugs, biologics, and medical devices. Currently, sponsors of covered studies must maintain many records with regard to clinical investigators, including protocol agreements and investigator resumes or curriculum vitae. FDA estimates than average of 15 minutes will be required for each recordkeeper to add this record to clinical investigators' file.

Table 3. -- Estimated Annual Recordkeeping Burden [1]

Section	Recordkeepers	Frequency per Recordkeeping	Records	Recordkeeper	
54.6	1,000	1	1,000	.25	250
Total					250

'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.

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 sponsors 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 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 physicians 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.	+ 2,965
Sponsors' total costs		$22,497

Clinical Investigators' co**sts:**

Reporting:	4,600 hours @ $87.69/hr.	$403,374

Total costs to sponsors and investigators $425,871

13. Estimates of Other Total Annual Cost to Respondents and Record Keepers

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. Annualized Cost to the 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 staffs 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 investigators 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 agencys 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	5,776.00
Total		$63,536.00

15. Explanation for Program Changes or Adjustments

ICRAS currently has only 1 respondent as currently approved, this number is not correct. Therefore, there is not an increase in response but a system-related error and does not reflect a revision in the agency estimate nor any program change. I have asked the helpdesk to correct.

16. Plans for Tabulation and Publication and Project Time Schedule

Results of this information collection will not be published.

17. Reason(s) Display of OMB expiration date is inappropriate

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

18. Exceptions to Certification for Paperwork Reduction Act Submissions

NA