

GUIDANCE FOR INDUSTRY

Financial Disclosure by Clinical Investigators

This guidance represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

I. Introduction

On February 2, 1998, FDA published a final rule requiring anyone who submits a marketing application of any drug, biological product or device to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the rule. This requirement, which became effective on February 2, 1999, applies to any clinical study submitted in a marketing application that the applicant or FDA relies on to establish that the product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety. This final rule requires applicants to certify to the absence of certain financial interests of clinical investigators or to disclose those financial interests. If the applicant does not include certification and/or disclosure, or does not certify that it was not possible to obtain the information, the agency may refuse to file the application. On December 31, 1998, FDA published an amended final rule that reduced the need to gather certain financial information for studies completed before February 2, 1999. On October 26, 1999, FDA published a draft guidance to provide clarification in interpreting and complying with these regulations. The burden hours required for Section 21 CFR Part 54 are reported and approved under OMB Control Number 0910 0396.

II. Financial Disclosure Requirements

Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), an applicant is required to submit to FDA a list of clinical investigators who conducted covered clinical studies and certify and/or disclose certain financial arrangements as follows:

1. Certification that no financial arrangements with an investigator have been made where study outcome could affect compensation; that the investigator has no proprietary interest in the tested product; that the investigator does not have a significant equity interest in the sponsor of the covered study; and that the investigator has not received significant payments of other sorts; and/or
2. Disclosure of specified financial arrangements and any steps taken to minimize the potential for bias.

Disclosable Financial Arrangements:

- A. Compensation made to the investigator in which the value of compensation could be affected by study outcome. This requirement applies to all covered studies, whether ongoing or completed as of February 2, 1999.
- B. A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement. This requirement applies to all covered studies, whether ongoing or completed as of February 2, 1999.
- C. Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. This requirement applies to all covered studies, whether ongoing or completed;
- D. Any equity interest in a publicly held company that exceeds \$50,000 in value. These must be disclosed only for covered clinical studies that are ongoing on or after February 2, 1999. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for 1 year following completion of the study; and
- E. Significant payments of other sorts, which are payments that have a cumulative monetary value of \$25,000 or more made by the sponsor of a covered study to the investigator or the investigators' institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study. This requirement applies to payments made on or after February 2, 1999.

Agency Actions

If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data including:

Initiating agency audits of the data derived from the clinical investigator in question;

Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on the overall study outcome;

Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

Definitions

Clinical Investigator - means any listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

Covered clinical study - means any study of a drug, biological product or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

Applicant - means the party who submits a marketing application to FDA for approval of a drug, device or biologic product or who submits a reclassification petition. The applicant is responsible for submitting the required certification and disclosure statements.

Sponsor of the covered clinical study - means the party providing support for a particular study at the time it was carried out.

III. PURPOSE

The financial disclosure regulations were intended to ensure that financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA are identified and disclosed by the applicant. FDA has received many questions concerning the implementation of this final rule. The agency is issuing this guidance to respond to these questions. FDA encourages applicants and sponsors to contact the agency for advice concerning specific circumstances that may raise concerns as early in the product development process as possible.

IV. QUESTIONS AND ANSWERS

1. Q. Why did FDA develop financial disclosure regulations?

A: In June 1991, the Inspector General of the Department of Health and Human Services submitted a management advisory report to FDA stating that FDA's failure to have a mechanism for collecting information on "financial conflicts of interest" of clinical investigators who study products that undergo FDA review could constitute a material weakness under the Federal Manager's Financial Integrity Act. Although FDA determined that a material weakness did not exist, the agency did conclude that there was a need to address this issue through rulemaking. During the rulemaking process, FDA also learned about potentially problematic financial arrangements through published newspaper articles, Congressional inquiries, public testimony, and comments. Based on the information gathered, FDA determined that it was appropriate to require the submission of certain financial information with marketing applications that include certain types of clinical data.

2. Q: Are applicants required to use FDA forms 3454 and 3455 in reporting this information?

A: Yes. The regulations require that the applicant submit one completed Form 3454 for all clinical investigators certifying to the absence of financial interests and arrangements. The applicant may append a list of investigator names to Form 3454 for those investigators certifying that those investigators hold none of the identifiable disclosable financial arrangements. For any clinical investigator for whom the applicant does not submit the certification, the applicant must submit a completed Form 3455 disclosing the financial interests and arrangements and steps taken to minimize the potential for bias.

Where an applicant cannot provide a blanket certification for all investigators because of the existence of disclosable financial arrangements for one or more investigators, an applicant should complete a disclosure form 3455 for each investigator having disclosable financial arrangements. The applicant should identify the specific covered clinical study (or studies) at issue and provide detailed information about the specific relationship that is being disclosed, (e.g., the nature of the contingent payment or the equity holdings of the investigator or the investigator's spouse or

dependent child that exceeded the threshold). This disclosure needs to be linked to the specific covered clinical study (or studies) in which the investigators participated.

In those instances where the applicant cannot provide complete certification or disclosure on all arrangements (e.g., the applicant has information about 2 of the 4 requirements but has been unable to obtain the rest of the information), the applicant should certify that despite the applicant's due diligence in attempting to obtain the information, the applicant was unable to obtain the information and should include an explanation of how the applicant attempted to obtain the information and why the information was not obtainable.

3. **Q: What does FDA mean by the term "due diligence"?**

A: "Due diligence" is a measure of activity expected from a reasonable and prudent person under a particular circumstance. In complying with these rules, sponsors and applicants should use reasonable judgement in deciding how much effort needs to be expended to collect this information. If sponsors/applicants find it impossible to obtain the financial information in question, applicants should explain why this information was not obtainable and document attempts made in an effort to collect the information.

4. **Q: Who, specifically, is responsible for signing the financial certification/disclosure forms?**

A: The forms are to be signed and dated by a responsible corporate official or representative of the applicant (e.g., the chief financial officer)

5. **Q. Where in a drug/biologic application should an applicant include certification that financial arrangements of concern do not exist or the disclosure of those arrangements that do exist? Where should the information be included in a device application?**

For drugs and biological product applications, applicants should include the financial certification/disclosure forms as part of item 19 (other) of the application. See form 356h. FDA is revising the current form 356h and upon completion of this revision, financial certification and disclosure information will become number 19 and (other) will become number 20. For device applications, applicants should submit the financial certification/disclosure forms according to the format outlined in the appropriate submission checklist.

6. **Q: What obligations do IND and IDE sponsors have regarding information collection prior to study start?**

A: The regulations, 21 CFR 312.53 and 21 CFR 812.43, provide that before permitting an investigator to begin participation in an investigation, the IND/IDE sponsor shall obtain sufficient accurate financial information that will allow an applicant to submit complete and accurate certification or disclosure statements required under Part 54. The sponsor is also required to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. By collecting the information prior to study start, the sponsor will be aware of any potential problems, can consult with the agency early on, and take steps to minimize the potential for bias. See question and answer 7 for additional information.

7. **Q: What is the responsibility of the IND/IDE sponsor for obtaining financial information from investigators at the IND/IDE stage when the IND/IDE sponsor is not the party who will be submitting a marketing application?**

The term "sponsor" has somewhat different meanings in the regulations at 312.53/812.43 and

54.2. An applicant must report financial interests in the sponsor of the covered study. Under 21 CFR 54.2, "sponsor" is defined as the party "supporting a particular study at the time it was carried out." FDA interprets support to include those who provide "material support", e.g., monetary support or test product under study. The sponsor of an IND or IDE, as defined in 21 CFR 312 and 812 is the "party or parties who take responsibility for and initiate a clinical investigation". The term "sponsor" is also used in 312.53 and 812.43 to refer to the party who will be submitting a marketing application (who is also responsible for submitting the certification and disclosure statement required by Part 54).

In most cases, the IND/IDE sponsor, the sponsor of the covered study, and the applicant company are the same party, but there are times where they may be different. For example, when an academic or government institution or CRO conducts a covered study and is the IND/IDE sponsor (Part 312/812 sponsor), a drug or device company that provides funding or the test article used in the study is a Part 54 sponsor, and is likely to be the applicant if a marketing application is submitted to FDA. If the drug or device company that was a sponsor of the covered study sold the drug/device to another company, the applicant could be neither the IND/IDE sponsor nor a Part 54 sponsor.

The responsibility for reporting financial information to FDA falls upon the applicant; that is, the final rule (Part 54) requires that the applicant company submit financial information on clinical investigators at the time the marketing application is submitted to the agency. The information that the applicant must report, apart from compensation that may be affected by study outcome and proprietary interests is:

1. equity interests in a Part 54 sponsor of a covered study (e.g., any interest that cannot be valued through reference to public prices and interest in excess of \$50,000 in a publicly held company), and
2. significant payments of other sorts by a Part 54 sponsor of a covered study.

Although reporting to the FDA is the responsibility of the applicant, the IND/IDE holder (part 312/812 sponsor) is required to collect the financial information before permitting an investigator to participate in a clinical study (312.53 and 812.43). The purpose of this requirement is two fold:

3. to alert the IND/IDE sponsor of the study to any potentially problematic financial interest as early in the drug development process as possible in order to minimize the potential for study bias and
4. to facilitate accurate collection of data that may be submitted many years later.

The IND/IDE sponsor, who is in contact with the investigator, is best placed to inquire as to the financial arrangements of investigators, and this obligation applies to any IND/IDE sponsor (e.g., commercial, government or CRO). The IND/IDE sponsor shall maintain complete and accurate records showing any financial interest as described in Section 54.4 (a) (3) (i-iv) in a sponsor of the covered study. The IND/IDE sponsor is responsible for ensuring that required financial information is collected and is made available to the applicant company, so that, the information can be included in the NDA/BLA/PMA submission.

8. **Q. The applicant is obligated to disclose financial interests related only to >covered studies, specifically those relied upon to provide support for the effectiveness of a product and certain others. An IND holder (IND sponsor), acting much earlier, must inquire into**

investigator financial interests before the ultimate role of a study in the application is determined. How will the IND sponsor determine which studies will ultimately require certification/disclosure statements?

A: The IND sponsor will need to consider the potential role of a particular study based on study size, design and other considerations. Almost any controlled effectiveness study could, depending on outcome, become part of a marketing application, but other studies might be critical too, such as a pharmacodynamic study in a population subset or a bioequivalence study supporting a new dosage form.

9. **Q. If a Contract Research Organization (CRO) is conducting a covered clinical study on behalf of another company, should the CRO collect the financial information from investigators? Is it necessary to collect financial information from investigators who have financial interests in CROs?**

A: With regard to CRO and commercial sponsor arrangements, the same principles as articulated in answer 6 would apply. For example, if a CRO meets the definition of an IND/IDE sponsor or has contracted to collect financial information from investigators on behalf of an IND/IDE sponsor, the CRO must collect financial information on clinical investigators' interests in Part 54 sponsors (312.53, 812.43). If the CRO provides material support for a covered study, financial information on clinical investigators' interests in the CRO is to be collected. If another entity provided material support for the study, the CRO also would collect financial information relative to that entity.

10. **Q: Suppose a public or academic institution conducts a study without any support from a commercial sponsor, but the study is then used by an applicant to support its marketing application. In that case, who is the "sponsor" of the study and what information should the applicant submit?**

A: In this case, the Part 54 sponsor of the study is the public or academic institution. Because such institutions are not commercial entities, in many instances, there will not be relevant equity interests to report. However, any relevant interests under 54.4, such as any proprietary interest in the tested product, including but not limited to a patent, trademark, copyright or licensing agreement are to be reported.

11. **Q: Does FDA have expectations about how the financial information should be collected? Will FDA consider it acceptable practice for a company to use a questionnaire to collect financial information from investigators rather than constructing an internal system to collect and report this information?**

A: FDA has no preference as to how this information is collected from investigators. Under this rule, sponsors/applicants have the flexibility to collect the information in the most efficient and least burdensome manner that will be effective, for example, through questionnaires completed by the clinical investigators or by using information already available to the sponsor. FDA does not require sponsors to establish elaborate tracking systems to collect the information.

12. **Q. What does FDA mean by the definition of clinical investigator and subinvestigator? Is it necessary to collect financial information on spouses and dependent children of subinvestigators?**

A: The definition of "clinical investigator" in Part 54 is intended to identify the individuals who should be considered investigators for purposes of reporting under the rule, generally, the people

taking responsibility for the study at a given study site. For drugs, biological products and devices, it should be noted that hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data are not meant to be included under the definition of clinical investigator. For purposes of this financial disclosure regulation, the term investigator also includes the spouse and each dependent child of the investigator and subinvestigator.

For drugs and biological products, clinical investigator means the individual(s) who actually conduct(s) and take(s) responsibility for an investigation, i.e. under whose immediate direction the drug or biologic is administered or dispensed to a subject or who is directly involved in the evaluation of research subjects. Where an investigation is directed by more than one person at a site, there may be more than one investigator who must report. For purposes of this rule, the terms investigators and subinvestigators include persons who fit any of these criteria: sign the Form FDA 1572, are identified as an investigator in initial submissions or protocol amendments under an IND, or are identified as an investigator in the NDA/BLA. For studies not conducted under an IND, the sponsor will need to identify the investigators and subinvestigators they consider covered by the rule in form 3454 and/or 3455. We expect that there will be at least one such person at each clinical site. If, however, there are other persons who are responsible for a study at a site, those persons should also be included as investigators.

For medical devices, clinical investigators are defined as individual(s), under whose immediate direction the subject is treated and the investigational device is administered, including follow-up evaluations and treatments. Where an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. In general, investigators and subinvestigators sign "investigator agreements" in accordance with 21 CFR 812.43(c) and it is these individuals whose interests should be reported. For studies not conducted under an FDA-approved IDE, (that is, a non-significant risk IDE or an exempt study), the sponsor would need to identify the investigators and subinvestigators they considered covered by the rule in form 3454 and 3455. We expect that there will be at least one such person at each site.

13. Q: Do the reporting requirements apply to efficacy studies that include large numbers of investigators and multiple sites? Will the agency consider a waiver mechanism to exempt applicants from collecting information from clinical investigators conducting these kinds of studies?

A: Large multi-center efficacy studies with many investigators are considered covered clinical studies within the meaning of the final rule. See 21 CFR 54.2(c). Data from investigators having only a small percentage of the total subject population (in a study with large numbers of investigators and multiple sites) may still affect the overall study results. For example, if a sponsor submitted data collected during a large, multi-center, double blind study that included several thousand subjects and a single clinical investigator at one of the largest sites enrolled one percent of subjects, that investigator could still be responsible for a significant number of subjects. If the investigator fabricated data or otherwise affected the integrity of the data, remaining data for the drug may not meet the statistical criteria for efficacy as defined prospectively in the protocol.

Because the regulations (see 21 CFR 312.10, 812.10, 314.90 and 814.20) allow a sponsor to seek a waiver of certain requirements, applicants may seek waivers of the financial disclosure requirements. FDA believes it is highly unlikely, however, that any waivers will be justified for studies begun after February 2, 1999, because the sponsor should already have begun collecting

the information on an ongoing basis. FDA will evaluate any request for waiver on a case-by-case basis.

14. **Q: The rule requires that investigators provide information on financial interests during the course of the study and for one year after completion of the study (see 54.4(b))? What does "completion of the study" mean?**

A: Completion of the study means that all study subjects have been enrolled and follow up of primary endpoint data on all subjects has been completed in accordance with the clinical protocol. Many studies have more than one stage (e.g., a study could have a short term endpoint and a longer term follow up phase). Completion of the study here refers to that part of the study being submitted in the application. If there were a subsequent application based on longer term data, completion of the study would be defined similarly for the new data. It is not required that an applicant submit updated financial information to FDA after submission of the application, but applicants must retain complete records. Where there is more than one study site, the sponsor may consider completion of the study to be when the last study site is complete, or may consider each study site individually as it is completed.

15. **Q: Do applicant companies need to collect information for a year after completion of the study? Who is responsible for collecting/providing this information?**

A: According to the February 2, 1998 final rule, the investigator must provide updated information when the investigator holds any equity interest in a privately held company or if stock holdings in a publicly held company exceed \$50,000 in value during the one year period following completion of the study. In addition, sponsors/applicants must keep records on file when significant payments of other sorts are paid by the sponsor of the covered study to the investigator or the investigator's institution to support activities of the investigator that have a cumulative monetary value of more than \$25,000, exclusive of the costs of conducting the covered clinical studies, during the study and for one year following completion of the study. FDA specified the one-year time frame because anticipation of payments may be as influential as payments already received. Applicants need only report on these arrangements when the marketing application is submitted, but sponsors/applicants are responsible for keeping updated financial information from the investigators in company files.

16. **Q: What information about a financial interest should be disclosed to the agency? For example, if an investigator owns more than \$50,000 of stock in a publicly held company, can the applicant just disclose that there is an interest that exceeds the \$50,000 threshold or is it necessary to disclose in written detail the arrangement in question?**

A: The applicant must disclose specific details of the financial interest including the size and nature of the financial interest in question and any steps taken to minimize the potential for study bias that such an interest represents.

17. **Q: Is the clinical investigator required to report all fluctuations above and below the \$50,000 level during the course of the investigation and one year after completion of the study?**

A: The rule requires sponsors/applicants to obtain financial information from clinical investigators and a commitment from clinical investigators to promptly update financial information, if any relevant changes occur during the course of the covered clinical study and for one year following the completion of the study [21 CFR 312.53(c)(4), 312.64(d), 812.43(c)(5), 812.110(d)]. In light of the potential volatility of stock prices, FDA recognizes that the dollar

value of an investigator's equity holding in a sponsoring/applicant company is likely to fluctuate during the course of a trial. Clinical investigators should report an equity interest when the investigator becomes aware that the holding has exceeded the threshold and the investigator should use judgement in updating and reporting on fluctuations in equity interests exceeding \$50,000. FDA does not expect the investigator to report when that equity interest fluctuates below that threshold.

18. Are equity interests in mutual funds and 401K(s) reportable?

A: Because an investigator would not have control over buying or selling stocks in mutual funds, these would not be reportable. In most circumstances, interests in 401K(s) would not be reportable, although equity interest in a product over \$50,000 would be reportable if it is a holding in a self directed 401K.

19. Q: Does the rule include ANDAs? Does the rule include 510(k)s that do not include clinical data?

A: The rule applies to any clinical study of a drug (including a biological product) or device submitted in a marketing application that the applicant or FDA relies on to establish that the product is effective, including studies of drugs that show equivalence to an approved product. This means that ANDAs are covered by the final rule. 510(k)s that do not include clinical data would not contain covered studies and therefore, no financial information from device manufacturers is needed for those applications.

20. Q: Do applicants need to provide information on investigators who participate in foreign studies?

A: Yes, applicants should include either a certification or disclosure of information for investigators participating in foreign covered studies. Where the applicant is unable to obtain the information despite acting with due diligence, the applicant may submit a statement documenting its efforts to obtain the information. In this case, it is unnecessary to submit a certification or disclosure form.

21. Q: Does the rule apply to studies in support of labeling changes?

A: The rule applies to studies submitted in a supplement when those studies meet the definition of a covered clinical study. It also applies to studies to support safety labeling changes where individual investigators make a significant contribution to the safety information.

22. Q: In the case where a subsidiary company of a larger parent company is conducting a covered clinical trial, is the applicant (subsidiary company) required to report information from clinical investigators about financial interests in only the subsidiary company, or is the applicant also required to report financial holdings, if any, of the investigator in the larger parent company?

A: If the subsidiary company meets the definition of sponsor of the covered study as defined under Part 54, the IND/IDE holder is required to collect from clinical investigators financial information related to the subsidiary company. The IND/IDE holder also must collect financial

information related to the parent company if the parent company is a Part 54 sponsor of the study in question. If there are multiple companies providing material support for a covered study, the IND/IDE holder is responsible for collecting financial information from clinical investigators related to all companies providing that support. The applicant company is ultimately responsible for submitting financial information to the Agency at the time the marketing application is submitted.

23. Q: Do "actual use studies" to support a request to switch a drug product from prescription to over-the-counter (OTC) status fit the definition of covered clinical study?

A: Applicants who file supplements requesting that FDA approve a switch of a prescription drug to OTC status or who file a new drug application for direct OTC use often conduct "actual use studies." These may be intended to demonstrate that the product is safe and effective when used without the supervision of a licensed practitioner; in other cases, they may test labeling comprehension or other aspects of treatment. Actual use studies performed to support these applications would be considered covered clinical studies if they were used to demonstrate effectiveness in the OTC setting or if it is a safety study where any investigator makes a significant contribution.

24. Q: Are clinical investigators of in vitro diagnostics (IVDs) covered under this regulation since they often involve specimens, not human subjects?

A: Yes. Applicants who submit marketing applications for IVDs must include the appropriate financial certification or disclosure information. Under section 21 CFR 812.3(p), "subject" is defined as a "human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control." Thus, an investigation of an IVD is considered a clinical investigation and, if it is used to support a marketing application, it would be subject to this regulation.

25. Q: How do significant payments of other sorts (SPOOS) relate to the variety of payments the sponsor might make to an individual or institution for various activities?

A: The term "significant payments of other sorts" was intended to capture substantial payments or other support provided to an investigator that could create a sense of obligation to the sponsor.

These payments do not include payments for the conduct of the clinical trial of the product under consideration or clinical trials of other products, under a contractual arrangement, but do include other payments made directly to the investigator or to an institution for direct support of the investigator. These payments would include honoraria, consulting fees, grant support for laboratory activities and equipment or actual equipment for the laboratory/clinic. This means that if an investigator were given equipment or money to purchase equipment for use in the laboratory/clinic, but not in relation to the conduct of the clinical trial, the payment would be considered a significant payment of other sorts and should be reported. If however, the investigator were provided with computer software or money to buy the software needed for use in the clinical trial, that would not need to be reported. Finally, payments made to the institution or to other nonstudy participating investigators that are not made on behalf of the investigator do not need to be reported.

26. Q: Are payments made to investigators to cover travel expenses (such as transportation, lodgings and meal expenses) trackable under significant payments of other sorts (SPOOS)?

A: Generally, reasonable payments made to investigators to cover reimbursable expenses such as

transportation, lodgings and meals do not fall within the purview of SPOOS and, therefore, would not need to be tracked. Travel costs associated with transporting, providing lodgings and meals for family members of investigators are considered unnecessary and should be tracked as SPOOS. In addition, other payments that exceed reasonable expectations, (for example, an investigator is flown to a resort location for an extra week of vacation) are considered outside of normal reimbursable expenditures and are not considered expenses that are necessary to conduct the study. Therefore, these types of expenses are also reportable and should be tracked as SPOOS.

27. Q: Under what circumstances would FDA refuse to file an application?

A: FDA may refuse to file any marketing application that does not contain either a certification that no specified financial arrangement exists or a disclosure statement identifying the specified arrangements or a statement that the applicant has acted with due diligence to obtain the required information, and an explanation of why it was unable to do so. The agency does not anticipate that it will be necessary to use its refuse to file authority often in the context of this financial disclosure rule. Applicants are encouraged to discuss their concerns on particular matters about financial information with FDA.

28. Q: Who will review a disclosure of the specified financial arrangements when such information is submitted in a marketing application? How will the financial information be handled during the review of the application?

A: Applicants are required to disclose specified financial information and any steps taken to minimize the potential for bias in any drug, biological product or device marketing application submitted to the agency on or after February 2, 1999. (See 21 CFR 54.4(a)(3)). FDA review staff, including project managers, consumer safety officers, medical officers and others in the supervisory chain will review this information on a case-by-case basis.

29. Q: Under what circumstances will FDA publicly discuss financial arrangements disclosed to the agency?

A: In the preamble to the final rule, FDA stated that certain types of financial information requested under the rule, notably clinical investigators' equity interests would be protected from public disclosure unless circumstances relating to the public interest clearly outweigh the clinical investigator's identified privacy interest. FDA cited the example of a financial arrangement so affecting the reliability of a study as to warrant its public disclosure during evaluation of the study by an advisory panel. FDA expects that only rarely would an investigator's privacy interest be outweighed by the public interest and thus warrant disclosure of the financial interest. It is difficult to predict all possible situations that may result in public disclosure of financial interests of a clinical investigator. The agency will carefully evaluate each circumstance on a case-by-case basis.

30. Q: Can FDA have access to documents related to financial disclosure or certification documents during an inspection?

A: Yes, FDA has the authority to have access to and to copy documents supporting an applicant's certification or disclosure statement submitted to the agency in a marketing application. Regulations implementing sections 505(i), 519, and 520(g) of the Act require sponsors to establish and maintain records of data (including but not limited to analytical reports by investigators) obtained during investigational studies of drugs, biological products, and devices, that will enable the Secretary to evaluate a product's safety and effectiveness. Under 54.6,

applicants must retain certain information on clinical investigators' financial interests and permits FDA employees to have access to and copy them at reasonable times.

31. Q: What kind of documentation is necessary for manufacturers to keep in case questions about certification and/or disclosure arise?

A: To the extent that applicants have relied on investigators as the source of information about potentially disclosable financial interests in any of the four categories, the underlying documentation -- e.g., copies of executed questionnaires returned by investigators, correspondence on the subject of financial disclosure, mail receipts, etc. should be retained. Likewise, to the extent that applicants who did not sponsor a covered clinical study rely on information furnished by the sponsor, the underlying documentation, including all relevant correspondence with and reports from the sponsor should be retained. To the extent that applicants rely upon information available internally, all appropriate financial documentation regarding the financial interests or arrangements in question should be retained. For example, in the case of "significant payments of other sorts," sponsors should keep documentation including, but not limited to, check stubs, canceled checks, records of electronic financial transactions, certified mail deliver receipts, etc.

32. Q: Where are forms FDA 3454 and 3455 located on the Web?

The forms are located at the following Internet address:
<http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>

33. Q: Who are the contact persons in each FDA Center to answer questions during this implementation phase?

The following persons may be contacted: Ms. Linda Carter in the Center for Drug Evaluation and Research, phone 301-594-6758, Dr. Joanne Less in the Center for Devices and Radiological Health, phone 301-594-1190, and Dr. Jerome Donlon in the Center for Biologics Evaluation and Research, phone 301-827-3028.

¹ This guidance has been prepared by the Implementation Team for Financial Disclosure comprised of individuals in the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), Center Biologics Evaluation and Research (CBER) and Center Devices and Radiological Health (CDRH) at the Food and Drug Administration.