

GUIDANCE FOR INDUSTRY

FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Radiological Health and Device Evaluation
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¹ GUIDANCE FOR INDUSTRY

Financial Disclosure by Clinical Investigators

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 the kinds of 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 a 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.

II. Financial Disclosure Requirements

Under this regulation (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.

¹This guidance has been prepared by the Implementation Team for Financial Disclosure comprised of individuals in the Office of the Commissioner, the Centers for Drug Evaluation and Research (CDER), Biologics Evaluation and Research (CBER) and Devices and Radiological Health (CDRH) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on financial disclosure by clinical investigators. 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.

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 as of February 2, 1999;
- D. Any equity interest in a publicly held company that exceeds \$50,000 in value 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 by clinical investigators 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 wishes to emphasize its commitment to work with sponsors as they begin their efforts to comply with the provisions of the rule. FDA also encourages applicants and sponsors to contact the agency for advice concerning the application of the rule to specific circumstances that may raise concerns and to do so 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 each marketing application that includes 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 a completed Form 3454 for all clinical investigators certifying to the absence of financial interests and 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.

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

A: FDA's regulations require the forms be signed and dated by a responsible corporate official or representative of the applicant (e.g., the chief financial officer).

4. **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?**

A: 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. 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 would need to provide disclosure information for each of these investigators and identify the specific covered clinical study (or studies) at issue. The applicant would complete disclosure form 3455 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). Applicants would also need to provide a certification form 3454 for all investigators for whom no financial disclosure is necessary. This certification needs to be linked to the specific covered clinical study (or studies) in which the investigators participated.

5. **Q: What does FDA mean by the definition "sponsor"?**

A: FDA means the party or parties who provide material support for a particular study at the time it is carried out (e.g., who provides funding and/or test articles needed to initiate the study).

6. **Q. If a Contract Research Organization (CRO) is conducting a covered clinical study, should the CRO or the sponsor collect the financial information from investigators? Should the CRO or the applicant sign the certification/disclosure forms?**

A: Under 21 CFR 54.4, clinical investigators subject to the IND or IDE regulations must provide sponsors with information needed to allow subsequent disclosure or certification. Whether or not the CRO collects the financial information from investigators and signs the forms depends upon the contractual responsibilities that have been transferred to the CRO. For example, if the CRO has assumed the responsibility for collecting the financial information from the investigator(s), then the CRO will collect that information per the contract. The applicant should sign the certification and/or disclosure forms.

7. **Q. Is it necessary to collect financial information from investigators who have financial interests in CROs?**

A: If the CRO is a sponsor of the covered study (providing material support for the study), then the investigator must report all financial arrangements in the CRO as consistent with the final rule. In addition, if the CRO is jointly supporting a covered study with the applicant company, the CRO is then acting as the sponsor of the covered study and under FDA's regulations, the investigator must report payments made by the CRO and applicant company to the investigator and financial holdings in both the CRO and the applicant company. (See question 5 for further clarification).

8. **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: As noted in the preamble to the rule, FDA believed that applicants/sponsors would have in their records, the information on all the reportable items with the exception of significant equity interests in publicly held companies that exceed \$50,000. During the public meetings that were held before the proposed and final rules were published, the issue of collecting the information, particularly for significant payments of other sorts, was not identified as a problem. However, during the early implementation phase of the financial disclosure rule, a number of pharmaceutical companies, especially those with many departments, subsidiaries and international components have advised FDA that they do not have such information readily available and would have to develop expensive new computer systems in order to collect this information. Thus, sponsors/applicants have asked FDA whether this information can be obtained from investigators through the use of questionnaires. Under this final rule, companies have the flexibility to collect the information in as efficient and least burdensome manner as possible. FDA has not required in the final rule that elaborate internal computerized tracking systems be constructed to collect this information, but does require that detailed records be maintained.

9. **Q: Should financial information be collected prior to study start?**

A: Yes. 21 CFR 312.53 and 21 CFR 812.43 state that before permitting an investigator to begin participation in an investigation, the sponsor shall obtain sufficient accurate financial information to allow the sponsor to submit complete and accurate verification or disclosure statements required under Part 54, and to commit 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. It is not required that an applicant submit new information to FDA after submission of the application, but applicants must retain complete records. By collecting the information prior to study start, the applicant/sponsor will be aware of any potential problems, can consult with the agency early on, and take steps to minimize the potential for bias.

10. **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: 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 and who is directly involved in the evaluation of research subjects. Where an investigation is conducted by a team of individuals, the investigator is the leader of the team. For purposes of this rule, the terms investigators and

subinvestigators include persons who: sign the Form FDA 1572 who are listed in item 6 of the Form FDA 1572, are identified in protocol amendments under an IND or are identified in the NDA/BLA as an investigator. 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.

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. "Subinvestigator" is not defined in 21 CFR Part 54 but includes those individuals participating in the clinical study and who perform functions such as administering the investigational device, conducting follow-up treatments or evaluations, and other significant patient care. In general, investigators and subinvestigators sign "investigator agreements" in accordance with 21 CFR 812.43 (c). For studies not conducted under an FDA-approved IDE, the sponsor would need to identify the investigators and subinvestigators they considered covered by the rule in form 3454 and 3455.

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. For purposes of this financial disclosure regulation, the term investigator also includes the spouse and each dependent child of the investigator and subinvestigator.

11. 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 multicenter 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 would still be responsible for a large 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.

12. **Q: The rule requires that investigators are required to 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 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.

13. **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 when stock holdings in a publicly held company exceed \$50,000 in value for one year 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. Sponsors and applicants need only report on these arrangements when the marketing application is submitted, but are responsible for keeping updated financial information from the investigators in company files.

14. **Q: What information about a financial interest should be disclosed to the agency? For example, if an investigator owns more than \$50,000 stock in a publicly owned 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: According to the February 2, 1998 final rule, the applicant must disclose 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 at the time the marketing application is submitted to FDA.

15. **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 from clinical investigators a commitment to inform the sponsor of any change in the investigator's financial information during the course of the covered clinical study and for one year after 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. For example, an investigator should report any sizable jump in value of equity interest to the sponsor or applicant of the covered study during the one year follow up period after completion of the study. FDA does not expect the investigator to report when that equity interest fluctuates below the threshold.

16. **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.

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

A: Yes, applicants must 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 its due diligence to do so, the applicant may submit a statement documenting its efforts in place of the certification or disclosure statement.

18. **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.

19. **Q: The regulation addresses compensation that may be affected by study outcome. Sponsors may provide bonuses or other incentives to investigators for recruiting subjects (e.g., a bonus to the investigator who enrolls the first 10 subjects, a bonus to the investigator who enrolls the most subjects, etc.). Is this considered compensation that may be affected by study outcome?**

A: The examples of payment arrangements described above do not meet the definition of compensation that may be affected by study outcome (which as used in the rule refers to study results) and therefore are not reportable under the rule.

20. **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 collect 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: Financial arrangements and interests of clinical investigators must be traced to the sponsor or applicant, if the applicant is acting as the sponsor of the covered study. If there are multiple companies providing material support for a covered study, financial arrangements must be reported in all companies providing that support since those companies will meet the definition of sponsor of the covered study. If the parent company is not providing material support for the study, the subsidiary company need not report on the investigator's interest in the parent company.

21. **Q: Do “actual use studies” to support a request to switch a drug product from prescription to over the counter 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.

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

A: Yes. Pursuant to FDA's regulations, 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.

23. Q: How do significant payments of other sorts 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 drug under consideration or clinical trials of other drugs, 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.

24. 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, especially during the early implementation phase of this rule.

25. 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. If FDA determines that a problematic financial interest exists, reviewers will consider whether the study design is sufficiently robust taking into account factors to protect against the introduction of bias such as independent data monitoring, multiple investigators, blinding, and independent endpoint assessment.

26. 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 a small number of clinical investigators will have financial interests that must be disclosed to FDA pursuant to the February 2, 1998 final rule; and of that number, 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 this on a case-by-case basis.

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

A: Yes, during an inspection, 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. 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. Section 704 authorizes officers or employees duly designated by the Secretary to inspect all records required to be kept under the foregoing sections.

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

A: In addition to letter and mail receipts, the applicant should retain complete records showing any financial interest or arrangement as described in the financial disclosure final rule(s) entered into between the applicant or sponsor of the covered study and the clinical investigator. In

addition to correspondence and copies of information provided by each investigator regarding his/her personal equity holdings and those of his/her families, applicants should retain appropriate financial documentation regarding the payments the applicant has made to investigators (for example, check stubs, canceled checks, records of direct electronic financial transactions, receipts of certified mail deliveries, etc.). If corporate policy prohibits the investigator from holding stock, the applicant should retain a copy of the policy statement, and may wish to obtain statements from the investigator that he/she adheres to the stated policy. These records must be retained for 2 years after the date of approval of the application and the person maintaining these records shall, upon request, permit an authorized officer or employee of FDA to have access to, copy and verify these records.

29. **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 Device Evaluation and Radiological Health, phone 301-594-1190, and Dr. Jerome Donlon in the Center for Biologics Evaluation and Research, phone 301-827-3028.